

Janssen Research & Development***Clinical Protocol**

A Phase 3, Multicenter, Randomized, Double-blind Placebo-controlled Study Evaluating the Efficacy and Safety of CNTO 1959 (Guselkumab) Delivered via a SelfDose™ Device in the Treatment of Subjects With Moderate to Severe Plaque-type Psoriasis

**Protocol CNTO1959PSO3006; Phase 3
Amendment 1****CNTO 1959 (guselkumab)**

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This compound has been investigated in Phase 3 clinical studies.

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	6 June 2016
Amendment 1	16 Nov 2016

Amendments below are listed beginning with the most recent amendment.

Amendment 1 (16 Nov 2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reasons for the amendment are to: 1) as requested by a health authority, include and describe the use of the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) as an additional safety assessment to be performed at screening, Week 0/baseline, and at each study visit post-baseline; 2) include an exclusion criterion related to the eC-SSRS assessment; 3) update the Time and Events Schedule to reflect addition of the eC-SSRS for assessment of suicide-related thoughts and behavior; 4) clarification that all shampoos used to treat psoriasis must also be reported on the subject electronic case report form (eCRF); 5) modification of a criterion to allow subjects who have completed antiviral treatment for hepatitis C virus (HCV) to participate; and 6) inclusion of data from the eC-SSRS in the safety analyses for the study and in the section for steps taken to assure data quality/quality control.

Applicable Section(s)	Description of Change(s)
Rationale: Based on health authority feedback, the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) will be included as a safety assessment at each study visit.	
Synopsis, Safety Evaluations	Safety evaluations include assessments of the following: adverse events (AEs, including injection site and allergic reactions), clinical laboratory tests (hematology, chemistry, and pregnancy testing), physical examinations, vital sign measurements, concomitant medication review, eC-SSRS questionnaires , and early detection of tuberculosis.
Rationale: Clarification of the Time and Events Schedule regarding how and when the Self-Injection Assessment Questionnaire (SIAQ) and the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) are to be completed during the study. Footnote h has been added regarding the use of the eC-SSRS; accordingly, old footnotes h and i have been re-numbered and are now i and j, respectively. Footnote k has been added regarding the eligibility requirements for participation in the study by a subject who tests positive for antibodies to hepatitis C at screening.	
Time and Events Schedule	<p>Safety Assessments (new category): eC-SSRS^h [Footnote h added to clarify that the eC-SSRS should be completed by the subject]: 1) as the first assessment at screening after signing informed consent and before any tests, procedures, or other consultations, 2) after the pre-SIAQ at Week 0/baseline and before any tests, procedures, or other consultations, and 3) as the first assessment for all post-baseline visits, before any tests, procedures, or other consultations to prevent influencing subject perceptions.</p> <p>Clinical Laboratory Assessments: Hepatitis B and C virus (HBV and HCV) serology Footnote k added to clarify that subjects who are seropositive for antibodies to hepatitis C virus (at screening) may be allowed to participate in the study provided they have 2 negative HCV RNA test results 6 months apart after completing antiviral treatment and prior to screening, and have a third negative HCV RNA test result at screening.</p>

Applicable Section(s)	Description of Change(s)
Rationale: Modification of a criterion to allow subjects who have completed antiviral treatment for hepatitis C virus (HCV) to participate if they have 2 negative HCV RNA test results 6 months apart after completing antiviral treatment and prior to screening, and have a third negative HCV RNA test result at screening.	
4.2 Exclusion Criteria Criterion #31.	Tests positive for hepatitis B virus (HBV) infection (Attachment 2) or is seropositive for antibodies to hepatitis C virus (HCV) at screening; unless they have 2 negative HCV RNA test results 6 months apart after completing antiviral treatment and prior to screening, and have a third negative HCV RNA test result at screening.
Rationale: Addition of a criterion for excluding subjects who have an eC-SSRS rating at screening indicative of unstable suicidal ideation or suicidal behavior who are confirmed to be at risk based on an evaluation by a mental health professional.	
4.2 Exclusion Criteria Criterion #38.	Has unstable suicidal ideation or suicidal behavior, that may be defined as an eC-SSRS rating at screening of: Suicidal ideation with intention to act (“4”), Suicidal ideation with specific plan and intent (“5”), or a suicide attempt (interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt) in the last 6 months and is confirmed to be at risk by the investigator based on an evaluation by a mental health professional. The final decision on excluding a subject will be made at the judgment of the investigator.
Rationale: Clarification that all shampoos used to treat psoriasis must be included in the list of all therapies, other than the study drug, that must be recorded in the electronic Case Report Form (eCRF).	
8. Concomitant Therapy Paragraph 2	All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements) different from the study drug, as well as all shampoos, moisturizers or emollients used to treat psoriasis , must be recorded in the eCRF.
Rationale: Clarification regarding the sequence in which planned assessments should be completed by the subject including the addition of the eC-SSRS questionnaire at screening.	
9.1.2. Screening Phase Paragraph 3	The recording of AEs and concomitant medications will start after the signing of the informed consent and will continue until the last study-related procedure has been completed. The eC-SSRS (‘Baseline/Screening’ version) should be completed after the subject signs consent but as the first assessment by the subject before any tests, procedures, or other consultations to prevent influencing subject perceptions.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification regarding the sequence in which planned assessments should be completed by the subject including the addition of the eC-SSRS at Week 0/randomization, the placebo-controlled period (Week 4 through 12), and the study drug treatment period (Weeks 16 through 32).	
9.1.4. Placebo-Controlled and Guselkumab Treatment Periods	<p>Week 0/Randomization</p> <p>Randomization visit procedures will be performed as specified in the Time and Events Schedule. The PRE self injection SIAQ (pre-SIAQ) should be completed by the subject first followed by the ‘Since Last Visit’ version of the eC-SSRS questionnaire in order to prevent influencing subject perceptions. All tests, procedures and other consultations will be performed after these questionnaires and before study agent administration (Section 9.5.1).</p> <p>At Week 0, if a mental health evaluation is required based on the Week 0 eC-SSRS score, either this evaluation must be conducted prior to randomization or, if not feasible, the subject should be screen-failed and then re-screened after a completed mental health evaluation, if appropriate (see Section 9.5.1).</p> <p>Week 4 through Week 12 (placebo-controlled period) and Week 16 through Week 32 (guselkumab treatment period)</p> <p>All visit procedures will be performed as specified in the Time and Events Schedule. The ‘Since Last Visit’ version of the eC-SSRS should be completed by the subject first before any tests, procedures, or other consultations at post-baseline study visits to prevent influencing subject perceptions (Section 9.5.1). All other study procedures and evaluations should be completed before the subject self-administers the study drug at each visit, except for the POST self injection SIAQ (post-SIAQ) at Weeks 4, 12, and 28 which must be completed by the subject after completion of study drug administration (Section 9.3.2) and the SelfDose Subject Questionnaire which must be completed after the POST self injection post-SIAQ (Section 9.3.3) at Week 12.</p>
Rationale: Clarification regarding the sequence in which planned assessments should be completed by the subject including the addition of the eC-SSRS questionnaire at the follow-up phase (Week 40).	
9.1.5. Follow-Up Phase	<p>Subjects will be followed for safety, efficacy, PK, and immunogenicity information through week 40 are indicated in the Time and Events Schedule. The ‘Since Last Visit’ version of the eC-SSRS should be completed by the subject first before any tests, procedures, or other consultations at the follow-up visit to prevent influencing subject perceptions (Section 9.5.1). If a subject discontinues study treatment before his or her last scheduled injection, procedures described in Section 10.2, Discontinuation of Study Treatment, should be followed.</p>
Rationale: The description of the SIAQ has been corrected to a 5 or 6-point Likert-type scale.	
9.3.2 Self-Injection Assessment Questionnaire Paragraph #2	The subject rates each item of the SIAQ on a 5 or 6-point semantic Likert-type scale.
Rationale: Addition of the eC-SSRS to the list of safety and tolerability assessments to be collected during the study.	
9.5. Safety Evaluations Paragraph 1	The safety and tolerability of study drugs (guselkumab and placebo) will be monitored by collecting information on AEs, including injection site and allergic reactions, clinical laboratory tests, physical examinations, vital sign measurements, eC-SSRS questionnaires , concomitant medication review, and early detection of TB at specified time points in the Time and Events Schedule and as described below.

Applicable Section(s)	Description of Change(s)
	<p>Rationale: A description of the eC-SSRS is provided as well as how and when this subject-completed questionnaire is to be used during the study, and the steps/actions that site staff should take to review the eC-SSRS findings report with a subject.</p>
9.5.1. Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)	<p>In light of the recent reports concerning suicidal ideation and behavior in patients with plaque psoriasis treated with an IL-17R antagonist (brodalumab), the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) will be used as a screening tool to prospectively evaluate the potential of guselkumab to induce suicidal ideation and behavior. The eC-SSRS defines five subtypes of suicidal ideation and behavior in addition to self-injurious behavior with no suicidal intent, and is a fully-structured, subject self-report C-SSRS questionnaire, including standardized questions, follow-up prompts, error handling routines, and scoring conventions.^{11,18} Two versions of the eC-SSRS will be used in this study, the ‘Baseline/Screening’ version and the ‘Since Last Visit’ version. The ‘Baseline/Screening’ version of the eC-SSRS will be conducted during the screening visit followed by the ‘Since Last Visit’ version of the eC-SSRS at all other visits through Week 40.</p> <p>Subjects will complete the eC-SSRS questionnaire using the sponsor-provided electronic tablets. Study site personnel will train the subjects on how to use the electronic device. The eC-SSRS will be provided in the local languages in accordance with local guidelines.</p> <p>The eC-SSRS will be performed during each evaluation visit according to the assessment schedule. During a visit, subjects will be directed to a private, quiet place with the electronic device to complete the assessment. Subjects who do not have suicidal behavior or ideation will answer a limited number of questions and will usually complete the assessment in about 3 minutes. Subjects with significant suicidal ideation and behavior may require up to 10 minutes to answer all relevant questions. The eC-SSRS will be performed first at the screening visit (after signing informed consent) after the pre-SIAQ at Week 0/baseline and before study agent administration. At all post-baseline visits, the eC-SSRS will be the first assessment/questionnaire that the subject must complete.</p> <p>At the conclusion of each assessment, the site will receive an eC-SSRS Findings Report. At screening and Week 0, subjects with a eC-SSRS score greater than 0 or a response to the question of “Self-injurious behavior without suicidal intent” other than ‘NO’ must be determined to be not at risk by the investigator based on an evaluation by a mental health professional in order to be randomized. Subjects with a score on the eC-SSRS that is greater than 0 or a response to the question of “Self-injurious behavior without suicidal intent” other than ‘NO’ at any post-baseline visit will also be referred to an appropriate mental health professional for evaluation. If a subject’s psychiatric disorder can be adequately treated with psychotherapy and/or pharmacotherapy then the subject, at the discretion of the investigator, should be continued with treatment. Ultimately, the determination of suicidality and risk is up to the investigator’s clinical judgment following evaluation by a mental health professional (e.g. psychiatrist, psychologist, or appropriately trained social worker or nurse).</p> <p>Positive reports are generated from the eC-SSRS vendor for ANY of the following findings:</p> <ul style="list-style-type: none"> • Suicidal ideation with intention to act (“4”) • Suicidal ideation with specific plan and intent (“5”) • Made suicide attempt • Interrupted suicide attempt

Applicable Section(s)	Description of Change(s)
	<ul style="list-style-type: none"> • Aborted suicide attempt • Preparatory behaviors for making a suicide attempt.
9.5.1. Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)—continued	<p>Negative suicidality indication reports are generated from the eC-SSRS vendor when there are NO indications of the above.</p> <p>The subject should not be released from the site until the eC-SSRS Findings Report (both for negative and positive reports) is reviewed by the investigator and the subject's risk has been assessed and follow-up determined, as appropriate.</p> <p>For each score, the following actions and associated alerts will be generated, if applicable:</p> <ul style="list-style-type: none"> • Score of 0: No further action is needed. • Score > 0: Subject risk assessed and referral to a mental health professional. <ul style="list-style-type: none"> ▪ Score of 1, 2, or 3: Negative findings report will be generated. ▪ Score of 4 or higher: Positive findings report will be generated. When the system reports that the subject has a positive suicidal indication (including for an incomplete assessment), the site will be immediately notified by fax/email and a telephone call from the eC-SSRS vendor. • Self-injurious behavior without suicidal intent = YES or 'Question Mark (ambiguous response)': Subject risk assessed and referral to a mental health professional. Negative findings report will be generated. <p>Interruption or the discontinuation of study treatment should be considered for any subject who reports suicidal ideation with intention to act ("4"), suicidal ideation with specific plan and intent ("5"), or a suicide attempt (interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt) on a post-baseline eC-SSRS assessment and who is deemed to be at risk by the investigator based upon evaluation by a mental health professional. Discussion of such subjects with the medical monitor or designee is required (See section 10.2). The final decision on suitability for continuing in the study will be made by the investigator.</p> <p>Any eC-SSRS finding, which in the opinion of the investigator is new or considered to be a worsening and clinically significant, should be reported on the AE eCRF (see section 12).</p>
Rationale: Addition of a criterion for discontinuation of study treatment for subjects who have a post-baseline eC-SSRS rating indicative of unstable suicidal ideation or suicidal behavior.	
10.2 Discontinuation of Study Treatment Bullet # 11	<ul style="list-style-type: none"> • Discontinuation of study treatment should be considered for subjects who report suicidal ideation with intention to act ("4"), suicidal ideation with specific plan and intent ("5"), or a suicide attempt (interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt) on a post-baseline eC-SSRS assessment. Discussion of such subjects with the medical monitor or designee is required. The final decision on suitability for continuing with study agent will be made by the investigator, based upon evaluation by a mental health professional.

Applicable Section(s)	Description of Change(s)
Rationale: Inclusion of the subject-completed eC-SSRS as a part of the safety analyses for adverse events in subjects who participate in the study.	
11.9. Safety Analyses	(Heading) Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)
Adverse Events	Suicide-related thoughts and behaviors based on the eC-SSRS will be summarized descriptively by treatment group.
Rationale: Inclusion of the subject-completed eC-SSRS as a component of the study-specific materials for investigators and site staff involved in the study.	
15. Study-Specific Materials	• Electronic Columbia-Suicide Severity Rating Scale
Bullet # 10	
Rationale: Inclusion of the subject-completed eC-SSRS as a part of the source documentation for the data obtained during the study.	
17.4. Source Documentation	Investigator-completed efficacy evaluations (IGA, PASI), the Observer Injection Checklist, and the subject-completed eC-SSRS will be recorded directly into an electronic tablet device during the visit at the study site. These data will be considered electronic source documentation.
Paragraph 5	
Rationale: Inclusion of the subject-completed eC-SSRS as a part of the steps to be taken for data quality assurance and quality control.	
17.6. Data Quality Assurance/Quality Control	Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, direct transmission of clinical laboratory data from a central laboratory, and direct transmission of efficacy data, eC-SSRS questionnaires , and the Observer Injection Checklist to the vendor database and then to the sponsor's database.
Paragraph 1	

SYNOPSIS

A Phase 3, Multicenter, Randomized, Double-blind Placebo-controlled Study Evaluating the Efficacy and Safety of CNTO 1959 (Guselkumab) Delivered via a SelfDose™ Device in the Treatment of Subjects With Moderate to Severe Plaque-type Psoriasis

Protocol Number: CNTO1959PSO3006

Guselkumab (CNTO 1959) is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody that binds to the p19 protein subunit of human interleukin (IL)-23 with high specificity and affinity. The binding of guselkumab to the IL-23p19 subunit blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23-specific intracellular signaling and subsequent activation and cytokine production. Guselkumab has been studied in Phase 1, Phase 2, and ongoing Phase 3 studies for the treatment of moderate to severe plaque psoriasis.

OBJECTIVES, ENDPOINTS, AND HYPOTHESES

Primary Objectives

- To evaluate the efficacy of guselkumab delivered using the SelfDose device for the treatment of subjects with moderate to severe plaque-type psoriasis.
- To assess the safety and tolerability of guselkumab delivered using the SelfDose device in subjects with moderate to severe plaque-type psoriasis.

Secondary Objectives

- To assess the pharmacokinetics (PK) and immunogenicity of guselkumab following subcutaneous administration using the SelfDose device in subjects with moderate to severe plaque-type psoriasis.
- To assess usability and acceptability of the SelfDose device.

Co-Primary Endpoints

- The proportion of subjects who achieve an Investigator's Global Assessment (IGA) score of cleared (0) or minimal (1) at Week 16.
- The proportion of subjects who achieve a Psoriasis Area and Severity Index (PASI) 90 response at Week 16.

Major Secondary Endpoints

- The proportion of subjects who achieve an IGA score of cleared (0) at Week 16.
- The proportion of subjects who achieve a PASI 100 response at Week 16.

Other Secondary Endpoints

- The proportion of subjects achieving an IGA score of mild or better (≤ 2) at Week 16.
- The proportion of subjects who achieve a PASI 75 response and a PASI 50 response at Week 16.
- The percent improvement from baseline in PASI response at Week 16.

- The proportion of subjects with successful, problem-free injections (assessment of usability) at Week 0.
- Self-Injection Assessment Questionnaire (SIAQ) domain scores for the 3 domains with items common to the SIAQ PRE- (Week 0) and POST- (Week 0 and Week 12) self-injection modules.
- Self-Injection Assessment Questionnaire POST-self-injection domain scores and change from baseline scores for each domain at Weeks 0, 4, 12, and 28.
- The proportion of subjects who had full delivery of the dose confirmed by inspection of the device at Weeks 4 and 12.

Additional Endpoints

- Serum guselkumab concentrations and antibodies to guselkumab will be analyzed to assess the PK and immunogenicity of guselkumab.
- Safety data will be summarized using descriptive statistics.
- Ratings for the SelfDose Subject Questionnaire will be summarized using descriptive statistics.

Hypotheses

The hypotheses are that guselkumab treatment delivered using the SelfDose device is superior to placebo as demonstrated by 1) the proportion of subjects achieving an IGA score of cleared (0) or minimal (1); and 2) the proportion of subjects achieving a PASI 90 response, both at Week 16.

OVERVIEW OF STUDY DESIGN

This is a Phase 3, randomized, double-blind, multicenter, placebo-controlled study evaluating the efficacy, safety, PK, immunogenicity, usability, and acceptability of guselkumab delivered using the SelfDose device in subjects with moderate to severe plaque-type psoriasis.

There are 2 database locks (DBLs) in this study, 1 at Week 20, and 1 at Week 40. The sponsor, with exception below, will be unblinded after the last subject has completed the Week 20 visit and the Week 20 DBL has occurred. The investigators, subjects, and sponsor site monitors will be unblinded after the last subject has completed the Week 40 visit, and the Week 40 DBL has occurred.

SUBJECT POPULATION

The target population is adult men or women with a diagnosis of plaque-type psoriasis (with or without psoriatic arthritis) for at least 6 months before the first administration of study drug. Subjects must have moderate to severe plaque-type psoriasis defined by PASI ≥ 12 , IGA ≥ 3 , and involved body surface area $\geq 10\%$. Subjects must be candidates for either systemic therapy or phototherapy for psoriasis, and may have previously received some systemic therapies or phototherapy for psoriasis.

DOSAGE AND ADMINISTRATION

Guselkumab 100 mg and liquid placebo for guselkumab will be provided in a single-use prefilled syringe assembled with a facilitated injection device referred to as the SelfDose device. The dose regimens are as follows:

- **Group I** (n=60): guselkumab 100 mg at Weeks 0, 4, 12, 20, and 28; placebo at Week 16 to maintain the study blind.
- **Group II** (n=15): placebo at Weeks 0, 4, and 12; cross over to guselkumab 100 mg at Weeks 16, 20, and 28.

EFFICACY EVALUATIONS

Efficacy evaluations include:

- Investigator's Global Assessment
- Psoriasis Area and Severity Index

USABILITY AND ACCEPTABILITY ASSESSMENTS

The usability and acceptability of the SelfDose device will be assessed using the Observer Injection Checklist and the subject-completed SIAQ, respectively.

PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

Venous blood samples will be collected for the measurement of serum guselkumab concentrations and detection of antibodies to guselkumab at the time points presented in the Time and Events Schedule. Serum samples will also be collected at the final visit from subjects who terminate study participation early.

SAFETY EVALUATIONS

Safety evaluations include assessments of the following: adverse events (AEs, including injection site and allergic reactions), clinical laboratory tests (hematology, chemistry, and pregnancy testing), physical examinations, vital sign measurements, concomitant medication review, eC-SSRS questionnaires, and early detection of tuberculosis. Safety data will be summarized using descriptive statistics.

STATISTICAL METHODS

A total of approximately 75 subjects randomized in a 4:1 ratio to guselkumab (n=60) and placebo (n=15) will have at least 99% power to detect differences for both co-primary endpoints at a significance level of 0.05. This sample size was also chosen to provide adequate power for major secondary endpoints.

For the primary analysis and major secondary analyses, all randomized and treated subjects will be included. For all the efficacy analyses, subjects will be analyzed according to the treatment group to which they were randomized, regardless of the treatment they actually received.

Primary Endpoint

The 2 co-primary endpoints will be compared between the guselkumab group and the placebo group. The analysis will be performed using a Fisher's exact test, 2-sided ($\alpha=0.05$).

Major Secondary Endpoints

The major secondary endpoints will be compared between the guselkumab group and the placebo group. The analyses will be performed using a Fisher's exact test, 2-sided ($\alpha=0.05$).

In order to control the overall Type 1 error rate, the primary analysis and major secondary analyses will be tested in a fixed sequence. That is, the first major secondary endpoint will be tested only if both co-primary endpoints are positive. Similarly, the second major secondary endpoint will be tested only if the first major secondary endpoint is positive.

Other Secondary Endpoints

Efficacy endpoints will be compared between the guselkumab group and the placebo group and nominal p-values will be provided.

Endpoints related to usability and acceptability will be summarized by treatment group and for the overall population.

Additional Endpoints

- Serum guselkumab concentrations over time will be summarized by treatment group using descriptive statistics.
- The incidence and titers of antibodies to guselkumab and incidence of neutralizing antibodies to guselkumab will be summarized.
- Safety data will be summarized using descriptive statistics.

TIME AND EVENTS SCHEDULE

Table 1: Time and Events Schedule												
	Phase	Screening ^a	Placebo-Controlled Period				Guselkumab Treatment Period					Follow-up ^b
	Week		0 (baseline) ^c	4	8	12	16	20	24	28	32	40
Study Procedures ^d												
Screening/Administrative												
Informed consent		X										
Inclusion/exclusion criteria		X	X									
Medical history and demographics		X										
Study Drug Administration												
Randomization			X									
Dispense/administer study drug ^e			X	X		X	X	X		X		
Safety Assessments												
Physical examination including skin examination			X								X	
Vital signs		X	X	X	X	X	X	X	X	X	X	
Weight			X									
Height			X									
Chest X-Ray		X										
eColumbia-Suicide Severity Rating Scale (eC-SSRS) ^h		X	X	X	X	X	X	X	X	X	X	
Pregnancy test – urine ⁱ		X	X	X		X	X		X		X	
Tuberculosis evaluation		X	X	X	X	X	X	X	X	X	X	
Concomitant therapy		X	X	X	X	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X	X	X	X	
Efficacy Assessments												
Body surface area (BSA)		X	X									
Investigator’s global assessment (IGA)		X	X	X	X	X	X	X	X	X	X	
Psoriasis Area and Severity Index (PASI)		X	X	X	X	X	X	X	X	X	X	
Usability and Acceptability Assessments												
Observer Injection Checklist (usability)			X									
Self-Injection Assessment Questionnaire (SIAQ; acceptability) ^g			X	X		X				X		
Device inspection to confirm delivery of complete dose			X	X		X	X	X		X		
Product Quality Complaints (PQCs)			X	X		X	X	X		X		
SelfDose Subject Questionnaire ^j						X						
Clinical Laboratory Assessments												

Table 1: Time and Events Schedule												
	Phase	Screening ^a	Placebo-Controlled Period				Guselkumab Treatment Period					Follow-up ^b
	Week		0 (baseline) ^c	4	8	12	16	20	24	28	32	40
Hematology ^j		X	X	X	X	X	X	X	X		X	X
Chemistry ^j		X	X	X	X	X	X	X	X		X	X
Lipid panel ^j			X									
QuantiFERON-TB test		X										
Hepatitis B and C virus (HBV and HCV) serology ^k		X										
Human immunodeficiency virus (HIV) antibody test		X										
High-sensitivity C-reactive protein (hs-CRP) ^j			X									
Pharmacokinetics and Immunogenicity												
Serum guselkumab concentration			X	X	X	X	X	X	X	X	X	X
Antibodies to guselkumab			X	X		X	X		X			X

a: The screening visit should occur within approximately 4 weeks prior to the Week 0 visit.

b: Week 40 assessments should be completed at least 12 weeks after the last study drug administration for subjects who discontinue study treatment or withdraw from the study as discussed in Sections 0 and Section 10.3, respectively.

c: Subjects must fast (ie, no food or beverages [except water]) for at least 8 hours before blood is drawn for lipid panel at Week 0.

d: All study procedures and evaluations should be completed before the subject self-administers the study drug, except for completion of the Observer Injection Checklist (during study drug administration) and the POST-self-injection SIAQ which must be completed after study drug administration.

e: Subjects will be trained to self-administer study injections at the study site using the SelfDose device and are required to self-administer all doses of study drug throughout the study.

f: Women of childbearing potential must have a negative urine pregnancy test before randomization, before study drug administration at applicable visits, and at Week 40 or at least 12 weeks after the last study drug administration for subjects who discontinue study treatment or withdraw from the study.

g: The SIAQ has 2 modules: PRE-self-injection to be completed prior to study drug administration at Week 0, and POST-self-injection to be completed after study drug administration at Weeks 0, 4, 12, and 28. At Week 0, the PRE-self-injection SIAQ should be completed by the subject before any tests, procedures, or other consultations to prevent influencing subject perceptions.

h: The eC-SSRS should be completed by the subject: 1) as the first assessment at screening after signing informed consent and before any tests, procedures, or other consultations, 2) after the pre-SIAQ at Week 0/baseline and before any tests, procedures, or other consultations, and 3) as the first assessment for all post-baseline visits, before any tests, procedures, or other consultations to prevent influencing subject perceptions.

i: Subjects will complete the SelfDose Subject Questionnaire after all study evaluations are completed, including after they self-inject study drug and after they have completed the POST-self-injection SIAQ at Week 12.

j: Laboratory tests are listed in Section 9.5, Safety Evaluations. All clinical laboratory samples should be collected prior to study drug administration. Details will be provided in the Laboratory Manual.

k: Subjects who are seropositive for antibodies to hepatitis C virus (at screening) may be allowed to participate in the study provided they have 2 negative HCV RNA test results 6 months apart after completing antiviral treatment and prior to screening, and have a third negative HCV RNA test result at screening.

ABBREVIATIONS

AE	adverse event
BCG	Bacille Calmette-Guérin
BQL	below the lowest quantifiable sample concentration of the assay
BSA	body surface area
CI	confidence interval
DBL	database lock
eDC	electronic data capture
eCRF	electronic case report form
eC-SSRS	electronic Columbia-Suicide Severity Rating Scale
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high density lipoprotein cholesterol
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN- γ	interferon gamma
IGA	Investigator's Global Assessment
IL	interleukin
IND	investigational new drug
IRB	Institutional Review Board
IWRS	interactive web response system
mAb	monoclonal antibody
MACE	major adverse cardiovascular event
NAbs	neutralizing antibodies
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
PASI	Psoriasis Area and Severity Index
PFS	prefilled syringe
PFS-U	prefilled syringe with an UltraSafe Plus™ Passive Needle Guard Delivery System
PGA	Physician's Global Assessment
PK	pharmacokinetic(s)
PQC	product quality complaint
PsA	psoriatic arthritis
qXw	every X weeks
RA	Rheumatoid Arthritis
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SIAQ	Self-Injection Assessment Questionnaire
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
Th	T helper
TNF α	tumor necrosis factor alpha

INTRODUCTION

Guselkumab (CNTO 1959) is a fully human immunoglobulin G1 lambda (IgG1 λ) monoclonal antibody (mAb) that binds to the p19 protein subunit of human interleukin (IL)-23 with high specificity and affinity. The binding of guselkumab to the IL-23p19 subunit blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23 specific intracellular signaling and subsequent activation and cytokine production. In this manner, guselkumab inhibits the biological activity of IL-23 in all in vitro assays examined.

Guselkumab is currently being studied using a prefilled syringe (PFS) in an UltraSafe Plus™ Passive Needle Guard Delivery System (PFS-U) in several Phase 2 and Phase 3 studies across several indications. This placebo-controlled study is designed to evaluate efficacy, safety, pharmacokinetic (PK), immunogenicity, usability, and acceptability using the PFS facilitated injection device referred to as the SelfDose™ device in subjects with moderate to severe plaque-type psoriasis which will be used to support the approval of the SelfDose presentation.

For the most comprehensive nonclinical and clinical information regarding guselkumab, refer to the latest version of the Investigator's Brochure and Addenda for guselkumab.

The term “sponsor” used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

1.1.1. Clinical Development of Guselkumab

The clinical development program to support use of guselkumab in the treatment of psoriasis includes one Phase 1 study in healthy subjects and in subjects with psoriasis, and one Phase 2 and three Phase 3 global studies. In addition, clinical studies have been or are being conducted in subjects with rheumatoid arthritis (RA) and psoriatic arthritis (PsA) as well as studies in subjects with palmoplantar pustulosis, generalized pustular psoriasis, or erythrodermic psoriasis conducted in Japan.

The following 3 global Phase 3 clinical studies of guselkumab in the treatment of moderate to severe plaque psoriasis are ongoing:

- CNTO1959PSO3001, a Phase 3 study to evaluate the efficacy and safety of guselkumab in subjects with moderate to severe plaque psoriasis.
- CNTO1959PSO3002, a Phase 3 study to evaluate the efficacy and safety of guselkumab in subjects with moderate to severe plaque psoriasis with randomized withdrawal and retreatment.
- CNTO1959PSO3003, a Phase 3 study to evaluate the efficacy and safety of guselkumab in subjects with moderate to severe plaque psoriasis and an inadequate response to ustekinumab.

One Phase 0 study (CNTO1959NAP0001) assessed the usability of a similar version of the SelfDose device in subjects with RA or psoriasis who self-injected placebo. A Phase 1 study (CNTO1959NAP1001) was also conducted to assess PK comparability of 2 formulations of guselkumab and to evaluate the PK comparability of guselkumab delivered by 2 different devices (PFS-U and SelfDose) in healthy subjects. One Phase 1 study (CNTO1959PSO1001) and one Phase 2 study (CNTO1959PSO2001) of guselkumab for the treatment of moderate to severe plaque-type psoriasis have been completed and demonstrated a favorable efficacy and safety profile for guselkumab. Relevant results from the Phase 0 study, the Phase 1 study comparing the 2 devices, and the Phase 2 study are presented below; details about the individual studies and Phase 1 efficacy and PK are provided in the Investigator's Brochure.

Phase 0 Study CNTO1959NAP0001

The design features and ability of subjects with RA or psoriasis to self-administer using a similar version of the SelfDose device were investigated in the randomized, single-center, open-label, Phase 0 study CNTO1959NAP0001. Subjects were randomized in a 1:1 ratio to 1 of 2 sequences of injection site locations (thigh-abdomen, abdomen-thigh) using randomized permuted blocks stratified by disease type (RA or psoriasis) and characteristics (presence or absence of hand impairment in RA group or body mass index [$<30 \text{ kg/m}^2$ or $\geq 30 \text{ kg/m}^2$] in the psoriasis group at screening).

The results of the study showed that subjects required little training to use the SelfDose device for self-administration without any assistance, and that the operation of the device was easy for subjects. Based on responses to questions related to their experience with the SelfDose device, subjects were confident in their ability to use the SelfDose device and were willing to self-administer medications with the device. They also accepted using the device on both their abdomen and thigh. Rheumatoid arthritis subjects with impaired hand function felt that SelfDose device seemed well-designed for arthritic patients. Subjects reported that it was easy to know when the injection was completed and that the full dose was delivered. No significant safety findings were observed. Three treatment-emergent injection site reactions of mild intensity and reasonably related (possibly, probably, or very likely related) to the SelfDose device were reported in the study in the psoriasis group: 2 events of injection site induration and 1 event of injection site erythema. No treatment-emergent adverse events (AEs) were reported in the RA group. No deaths, serious adverse events (SAEs), or AEs leading to discontinuation were reported during the study.

Phase 1 Study CNTO1959NAP1001

CNTO1959NAP1001 was a study conducted to assess the PK comparability of guselkumab in liquid formulation versus the lyophilized formulation as well as to assess the PK comparability of guselkumab in liquid formulation with 2 different delivery devices (PFS-U and SelfDose). In this Phase 1 study, a large inter-subject variability in systemic exposure to guselkumab was observed in each delivery device group. With respect to the comparison of PK of guselkumab between the 2 different delivery devices (PFS-U and SelfDose) with the same liquid formulation, the ratios of the geometric means of the maximum observed serum concentration (C_{\max}) and area under the serum concentration versus time curve (AUC) from the liquid formulation with

SelfDose (Test) to those from the liquid formulation with PFS-U (Reference) were slightly greater than 1 (1.18 to 1.20), nevertheless, the 90% confidence intervals (CIs) for the geometric mean ratios were still within the interval of 0.70 to 1.43. It should be noted that despite the fact that the guselkumab exposures of the SelfDose and PFS-U devices were not technically equivalent based on ratios of the geometric means and 90% CIs, there was substantial overlap in the distribution of systemic exposure between the PFS-U and SelfDose groups.

With respect to safety of the 2 different devices, the incidence of treatment-emergent AEs was 73.2% in the SelfDose group and 65.0% in the PFS-U group. Incidence of injection site reactions was higher in the SelfDose group (51.2%) compared with the PFS-U group (25.0%); the most commonly reported injection site reactions in the SelfDose and PFS-U groups were erythema (51.2% and 25.0%, respectively), induration (22.0% and 7.5 %, respectively), and pain (12.2% and 12.5%, respectively). No deaths or AEs leading to discontinuation occurred during the study.

Phase 2 Study CNT01959PSO2001 (X-PLORE)

In the X-PLORE study, 293 subjects with moderate to severe plaque-type psoriasis were randomized to receive 1 of 5 guselkumab subcutaneous (SC) dose regimens (5 mg at Weeks 0, 4, and then every 12 weeks [q12w], 15 mg every 8 weeks [q8w], 50 mg at Weeks 0, 4, and then q12w, 100 mg q8w, or 200 mg at Weeks 0, 4, and then q12w), placebo, or adalimumab (HUMIRA®) 80 mg at Week 0, 40 mg at Week 1, and then 40 mg every 2 weeks (q2w).

The proportions of subjects who achieved a Physician's Global Assessment (PGA) score of cleared (0) or minimal (1) were significantly higher at Week 16 in all guselkumab treatment groups compared with the placebo group. In addition, higher proportions of subjects in the guselkumab 50 mg q12w, 100 mg q8w, and 200 mg q12w groups achieved a PGA score of 0 or 1 compared with the adalimumab group at Week 16. Improvements in psoriasis were demonstrated at Week 4 in the guselkumab groups and continued to improve through Week 16. A dose-response in efficacy was observed up to 100 mg q8w; the proportions of subjects who achieved a PGA score of 0 or 1 were similar in the 100 mg q8w and 200 mg q12w dose groups. Results for improvements in Psoriasis Area and Severity Index (PASI) scores were generally similar to those observed for PGA.

Treatment with guselkumab was generally well-tolerated through Week 52. The proportions of subjects with 1 or more AEs were comparable across the combined guselkumab, placebo, and the adalimumab groups through Week 16, with no evidence of a dose-response in the occurrence of AEs across the guselkumab groups. The most common events in the combined guselkumab group were nasopharyngitis, headache, and upper respiratory tract infection. Through Week 16, the proportion of subjects with 1 or more SAEs was low across all treatment groups. Two serious infections (guselkumab 50 mg group), no malignancies, and no major adverse cardiovascular events (MACE) were reported. Similar patterns of AEs were observed through Week 52. Events of interest through Week 52 included the 2 serious infections noted through Week 16, 1 malignancy in the 200 mg q12w group, and 3 MACE (1 in the 5 mg q12w group and 2 in the 100 mg q8w group).

Approximate dose-proportionality in serum guselkumab concentrations through Week 52 was observed after multiple SC administrations at dose levels ranging from 15 to 200 mg. Steady-state serum guselkumab concentrations were achieved by approximately Week 16 for both the q8w and q12w regimens. In each treatment group, mean or median trough serum guselkumab concentrations were maintained at steady state through Week 40 (q8w groups) or Week 52 (q12w groups). There was no evidence of accumulation in serum guselkumab concentrations over time with SC q8w or q12w administrations. Serum guselkumab concentrations appeared to be affected by subject body weight; higher-weight subjects (>90 kg) had lower mean steady-state trough serum guselkumab concentrations compared with lower-weight subjects (≤90 kg).

The overall incidence of antibodies to guselkumab across all guselkumab treatment groups through Week 52 was 6.3%, with generally low titers. None of the subjects who were positive for antibodies to guselkumab had antibodies that were able to neutralize the bioactivity of guselkumab in vitro. No consistent impact of antibodies to guselkumab on serum guselkumab concentrations was observed across the guselkumab treatment groups.

1.1.2. SelfDose Device

The guselkumab presentation used in this Phase 3 psoriasis clinical study is a prefilled 1 mL glass syringe with a 27 gauge, 1/2 inch-long thin-wall needle as the primary drug container referred to as the PFS. This PFS is assembled with a facilitated injection device and in combination is referred to as the SelfDose device. This same PFS is used for assembly with the UltraSafe Plus device for the PFS-U presentation. The sponsor intends to seek approval for guselkumab as a single-use, SC self-administered product in the SelfDose presentation.

The SelfDose device is a manually operated, disposable device designed to insert the PFS needle to a fixed depth and to deliver the contents of a PFS for SC injection. The device incorporates a needle safety guard that automatically locks over and shields the needle after injection to prevent accidental needle sticks. By design, the SelfDose device is highly intuitive and eliminates user difficulties that have been associated with auto-injector actuation button interlocks and with premature removal of the device from the skin prior to completion of an auto-injector's delivery cycle. Additional details describing the SelfDose device are provided in the Site Investigational Product Procedures Manual.

1.2. Overall Rationale for the Study

1.2.1. Role of Interleukin-23 in the Treatment of Psoriasis

IL-23 is a member of the IL-12 family of heterodimeric cytokines. IL-23 shares the p40 subunit with IL-12. However, in contrast to IL-12, which is formed from p40/p35 heterodimers, the p40 subunit is paired with a p19 subunit to form IL-23.¹³ Although IL-12 and IL-23 are closely related cytokines, which are expressed by antigen-presenting cells such as dendritic cells, increasing evidence suggests that these 2 cytokines drive divergent immunological pathways. IL-12 induces the production of interferon-gamma (IFN-γ) producing T helper 1 (Th1) cells, which are important in host defense to intracellular pathogens by promoting cytotoxic,

antimicrobial, and antitumor responses. IL-23, alone or in combination with other cytokines (transforming growth factor β [TGF- β] and IL-6 or IL-1 β), drives the expansion and/or maintenance of mouse and human CD4⁺ IL-17 producing T helper 17 (Th17) cells. Th17 cells produce the pro-inflammatory cytokines, IL-17A, IL-17F, IL-22, IL-6, and tumor necrosis factor alpha (TNF α).^{2,6,21}

Guselkumab, a human mAb directed against the p19 subunit of IL-23 specifically targets IL-23. A rapidly growing body of literature suggests that the IL-23/IL-17 pathway contributes to the chronic inflammation underlying the pathophysiology of many immune-mediated diseases,^{15,20} including psoriasis,⁹ inflammatory bowel disease, ankylosing spondylitis, and PsA. In addition, susceptibility to psoriasis, PsA, and inflammatory bowel disease has been shown to be associated with genetic polymorphisms in IL-23/IL-23R components.^{1,3,8,12,14} Finally, the clinical response to guselkumab observed in Phase 1 and Phase 2 psoriasis studies demonstrates the specific importance of IL-23 in the pathogenesis of plaque psoriasis and supports further investigation in Phase 3 clinical studies.

1.2.2. Dose Justification

A dose regimen of guselkumab 100 mg at Weeks 0 and 4 and q8w thereafter was selected for the global Phase 3 studies of guselkumab for the treatment of moderate to severe plaque-type psoriasis and will also be utilized in this study. This dose regimen was chosen based on results of the guselkumab dose-ranging study (CNTO1959PSO2001) in subjects with moderate to severe plaque-type psoriasis and PK/pharmacodynamic modeling based on the data from that study.

1.2.3. Device Justification

The SelfDose is a manually operated, disposable device designed to manually insert the needle of a PFS to a fixed depth and to deliver the contents of a PFS for SC injection. The SelfDose presentation of guselkumab uses the same PFS as the UltraSafe PlusTM Passive Needle Guard (UltraSafe Plus) presentation that is currently being used in Phase 3 global clinical trials. Though both the SelfDose and the UltraSafe Plus are effective needle safety devices intended to shield the needle after injection to prevent accidental needle sticks, the SelfDose further incorporates usability features that make the device simple and intuitive to use. In addition, the usability of the SelfDose device has been established in several formative human factors studies, a summative human factors study, and an actual use study (CNTO1959NAP0001). Of note, the SelfDose device to be used in this study differs slightly from that used in previous studies (CNTO1959NAP0001, CNTO1959NAP1001) in order to yield a needle injection depth similar to the PFS. This change is expected to decrease the small PK differences observed between the SelfDose and PFS-U devices in the CNTO1959NAP1001 study.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESES

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objectives

The primary objectives are:

- To evaluate the efficacy of guselkumab delivered using the SelfDose device for the treatment of subjects with moderate to severe plaque-type psoriasis.
- To assess the safety and tolerability of guselkumab delivered using the SelfDose device in subjects with moderate to severe plaque-type psoriasis.

Secondary Objectives

The secondary objectives are:

- To assess the PK and immunogenicity of guselkumab following SC administration using the SelfDose device in subjects with moderate to severe plaque-type psoriasis.
- To assess usability and acceptability of the SelfDose device.

2.1.2. Endpoints

Co-Primary Endpoints

- The proportion of subjects who achieve an Investigator's Global Assessment (IGA) score of cleared (0) or minimal (1) at Week 16.
- The proportion of subjects who achieve a PASI 90 response at Week 16.

Major Secondary Endpoints

- The proportion of subjects who achieve an IGA score of cleared (0) at Week 16.
- The proportion of subjects who achieve a PASI 100 response at Week 16.

Other Secondary Endpoints

- The proportion of subjects achieving an IGA score of mild or better (≤ 2) at Week 16.
- The proportion of subjects who achieve a PASI 75 response and a PASI 50 response at Week 16.
- The percent improvement from baseline in PASI response at Week 16.
- The proportion of subjects with successful, problem-free injections (assessment of usability) at Week 0.
- Self-Injection Assessment Questionnaire (SIAQ) domain scores on the 3 domains with items common to the SIAQ PRE- (Week 0) and POST- (Week 0 and Week 12) self-injection modules.

- Self-Injection Assessment Questionnaire POST-self-injection domain scores and change from baseline scores for each domain at Weeks 0, 4, 12, and 28.
- The proportion of subjects who had full delivery of the dose confirmed by inspection of the device at Weeks 4 and 12.

Additional Endpoints

- Serum guselkumab concentrations and antibodies to guselkumab will be analyzed to assess the PK and immunogenicity of guselkumab.
- Safety data will be summarized using descriptive statistics
- Ratings for the SelfDose Subject Questionnaire will be summarized using descriptive statistics.

2.2. Hypotheses

The hypotheses are that guselkumab treatment delivered using the SelfDose device is superior to placebo as demonstrated by 1) the proportion of subjects achieving an IGA score of cleared (0) or minimal (1); and 2) the proportion of subjects achieving a PASI 90 response, both at Week 16.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a Phase 3, randomized, double-blind, multicenter, placebo-controlled study evaluating the efficacy, safety, PK, immunogenicity, usability, and acceptability of guselkumab delivered using the SelfDose device in subjects with moderate to severe plaque-type psoriasis. The target population is adult men or women, with a diagnosis of plaque-type psoriasis (with or without PsA) for at least 6 months before the first administration of study drug. Subjects must have moderate to severe plaque type psoriasis defined by PASI ≥ 12 , IGA ≥ 3 , and involved body surface area (BSA) $\geq 10\%$. Subjects must be candidates for either systemic therapy or phototherapy for psoriasis, and may have previously received some systemic therapies (Section 4.1, Inclusion Criteria, 4.2, Exclusion Criteria) or phototherapy for psoriasis. Subjects with nonplaque forms of psoriasis (eg, erythrodermic, guttate, or pustular) or with drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium) are excluded. Subjects who have ever received guselkumab are also excluded.

Approximately 75 subjects who satisfy all inclusion and exclusion criteria will be randomized in a 4:1 ratio to 1 of 2 arms:

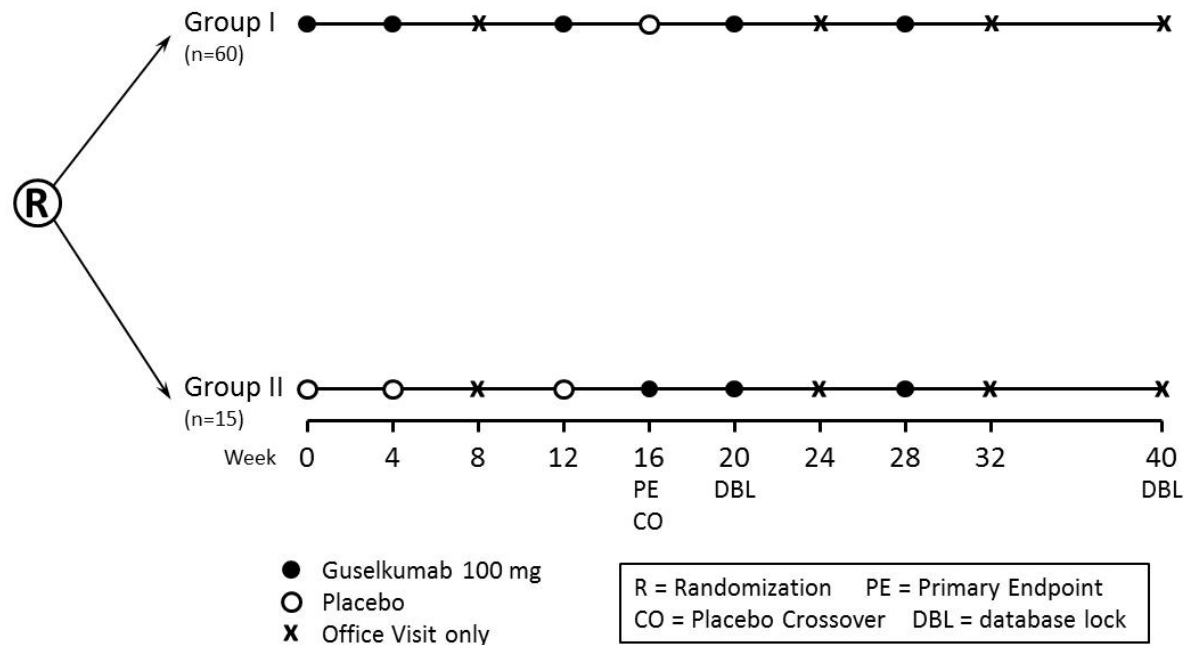
- **Group I** (n=60): guselkumab 100 mg at Weeks 0, 4, 12, 20, and 28; placebo at Week 16 to maintain the study blind.
- **Group II** (n=15): placebo at Weeks 0, 4, and 12; cross over to guselkumab 100 mg at Weeks 16, 20, and 28.

Week 28 is the last dosing visit; subjects will be followed for an additional 12 weeks and have a final safety visit at Week 40. The end of the study is defined as the time the last subject completes the Week 40 visit.

There are 2 database locks (DBLs) in this study, 1 at Week 20, and 1 at Week 40.

A diagram of the study design is provided below in [Figure 1](#).

Figure 1: Schematic Overview of the Guselkumab SelfDose Device Study



3.2. Study Design Rationale

As described in Section 1.2.1, there is substantial scientific and clinical evidence supporting the critical role of IL-23 in the pathogenesis of psoriasis. Specifically, the clinical response to guselkumab observed in Phase 1 and Phase 2 psoriasis studies provides compelling evidence of the specific importance of this cytokine.

In this study, subjects will self-administer guselkumab using the SelfDose device (Section 1.1.2) to assess the usability and acceptability of the device in administration of study drug.

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment. Primary comparisons are planned between guselkumab and placebo at Week 16, which is within the range that has been used in previous studies of biologic therapies for psoriasis (12 to 16 weeks).^{7,10,16,19} Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of

statistical comparisons across treatment groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within approximately 4 weeks before administration of the study drug.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

For a discussion of the statistical considerations of subject selection, refer to Section [11.2](#), Sample Size Determination.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Be a man or a woman at least 18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place).
2. Have a diagnosis of plaque-type psoriasis (with or without PsA) for at least 6 months before the first administration of study drug.
3. Have a PASI ≥ 12 at screening and at baseline.
4. Have an IGA ≥ 3 at screening and at baseline.
5. Have an involved BSA $\geq 10\%$ at screening and at baseline.
6. Be a candidate for phototherapy or systemic treatment for psoriasis (either naïve or history of previous treatment).
7. Before randomization, a woman must be either:
 - Not of childbearing potential: premenarchal; postmenopausal (>45 years of age with amenorrhea for at least 12 months or any age with amenorrhea for at least 6 months and a serum follicle-stimulating hormone level (FSH) >40 IU/L); permanently sterile (eg, tubal occlusion, hysterectomy, bilateral salpingectomy); or otherwise be incapable of pregnancy.
 - Of childbearing potential and practicing a highly effective method of birth control, consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: eg, established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device (IUD) or intrauterine system (IUS); barrier methods: condom or occlusive cap (diaphragm or cervical/vault caps) plus spermicidal foam/gel/film/cream/suppository (if available in their locale); male partner sterilization (the

vasectomized partner should be the sole partner for that subject); true abstinence (when this is in line with the preferred and usual lifestyle of the subject).

Note: If a female subject's childbearing potential changes after start of the study (eg, a woman who is not heterosexually active becomes active, a premenarchal woman experiences menarche), she must begin practicing a highly effective method of birth control, as described above.

8. A woman of childbearing potential must have a negative urine pregnancy test (β -human chorionic gonadotropin [β -hCG]) at screening and at Week 0.
9. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for at least 12 weeks after receiving the last administration of guselkumab.
10. A man who is sexually active with a woman of childbearing potential and who has not had a vasectomy must agree to use a barrier method of birth control (eg, either a condom [with spermicidal foam/gel/film/cream/suppository if available in their locale] or a partner with an occlusive cap [diaphragm or cervical/vault caps] plus spermicidal foam/gel/film/cream/suppository if available in their locale), during the study and for at least 12 weeks after receiving the last administration of guselkumab. All men must also agree to not donate sperm during the study and for at least 12 weeks after receiving the last administration of guselkumab.
11. Are considered eligible according to the following tuberculosis (TB) screening criteria:
 - Have no history of latent or active TB prior to screening. An exception is made for subjects who have a history of latent TB and satisfy 1 of the following 3 criteria:
 - are currently receiving treatment for latent TB
 - will initiate treatment for latent TB prior to first administration of study drug
 - have documentation of having completed appropriate treatment for latent TB within 5 years prior to the first administration of study drug. It is the responsibility of the investigator to verify the adequacy of previous anti-TB treatment and provide appropriate documentation.
 - Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.
 - Have had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB prior to the first administration of study drug.
 - Within 2 months prior to the first administration of study drug, have a negative QuantiFERON[®]-TB Gold test result (see [Attachment 1](#)), or have a newly identified positive QuantiFERON-TB Gold test result in which active TB has been ruled out and for which appropriate treatment for latent TB (see [Section 9.1.2](#), Screening Phase) has been initiated prior to the first administration of study agent.

- Indeterminate results should be handled as outlined in Section 9.1.2, Screening Phase.

NOTE: The QuantiFERON-TB Gold test is not required at screening for subjects with a history of latent TB and ongoing treatment for latent TB or documentation of having completed adequate treatment as described above; subjects with documentation of having completed adequate treatment as described above are not required to initiate additional treatment for latent TB.

- Have a chest radiograph (both posterior-anterior and lateral views), taken within 3 months prior to the first administration of study drug and read by a qualified radiologist, with no evidence of current, active TB or old, inactive TB.
- Agree not to receive a live virus or live bacterial vaccination during the study, or within 3 months after the last administration of study drug. For information on Bacille Calmette-Guérin (BCG) vaccination, see Inclusion Criterion 13.
 - Agree not to receive a BCG vaccination during the study, or within 12 months after the last administration of study drug.
 - Have screening laboratory test results within the following parameters, if one or more of the laboratory parameters is out of range, a single retest of laboratory values is permitted:
 - Hemoglobin ≥ 10 g/dL (SI: ≥ 100 g/L)
 - White blood cells $\geq 3.5 \times 10^3/\mu\text{L}$ (SI: ≥ 3.5 GI/L)
 - Neutrophils $\geq 1.5 \times 10^3/\mu\text{L}$ (SI: ≥ 1.5 GI/L)
 - Platelets $\geq 100 \times 10^3/\mu\text{L}$ (SI: ≥ 100 GI/L)
 - Serum creatinine ≤ 1.5 mg/dL (SI: ≤ 135 $\mu\text{mol/L}$)

Aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels must be $\leq 2 \times$ upper limit of normal for the laboratory conducting the test.
 - Agree to avoid prolonged sun exposure and avoid use of tanning booths or other ultraviolet light sources during study.
 - Be willing and able to adhere to the prohibitions and restrictions specified in this protocol.
 - Be willing to self-administer study drug independently and assessed by the investigator as physically able to do so.
 - Must sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. Has a history or current signs or symptoms of severe, progressive, or uncontrolled renal, cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric, or metabolic disturbances.
2. Has unstable cardiovascular disease, defined as a recent clinical deterioration (eg, unstable angina, rapid atrial fibrillation) in the last 3 months or a cardiac hospitalization within the last 3 months.
3. Currently has a malignancy or has a history of malignancy within 5 years before screening (with the exception of a non-melanoma skin cancer that has been adequately treated with no evidence of recurrence for at least 3 months before the first study drug administration or cervical carcinoma in situ that has been treated with no evidence of recurrence for at least 3 months before the first study drug administration).
4. Has a history of lymphoproliferative disease, including lymphoma; a history of monoclonal gammopathy of undetermined significance (MGUS); or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy or splenomegaly.
5. Has a history of chronic or recurrent infectious disease, including but not limited to chronic renal infection, chronic chest infection (eg, bronchiectasis), recurrent urinary tract infection (recurrent pyelonephritis or chronic nonremitting cystitis), fungal infection (mucocutaneous candidiasis), or open, draining, or infected skin wounds or ulcers.
6. Has a transplanted organ (with exception of a corneal transplant >3 months before the first administration of study drug).
7. Has a history of an infected joint prosthesis, or has received antibiotics for a suspected infection of a joint prosthesis, if that prosthesis has not been removed or replaced.
8. Has or has had a serious infection (eg, sepsis, pneumonia, or pyelonephritis), or has been hospitalized or received intravenous antibiotics for an infection during the 2 months before screening.
9. Has or has had herpes zoster within the 2 months before screening.
10. Is pregnant, nursing, or planning a pregnancy (both men and women) while enrolled in the study or within 12 weeks following the last administration of study drug.
11. Has a nonplaque form of psoriasis (eg, erythrodermic, guttate, or pustular).

12. Has current drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium).
13. Has previously received guselkumab.
14. Has received any anti-TNF α biologic therapy within 3 months before the first administration of study drug.
15. Has received any therapeutic agent directly targeted to IL-12, IL-17, or IL-23 within 6 months before the first administration of study drug (including but not limited to ustekinumab, tildrakizumab [MK3222], risankizumab [BI-655066], secukinumab [AIN457], ixekizumab [LY2439821], or brodalumab [AMG827]).
16. Has received natalizumab, belimumab, or agents that modulate B cells or T cells (eg, rituximab, alemtuzumab, abatacept, or visilizumab) within 12 months before the first administration of study drug.
17. Has received any systemic immunosuppressants (eg, methotrexate, azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, tacrolimus) or anakinra within 4 weeks before the first administration of study drug.
18. Has received phototherapy or any systemic medications/treatments that could affect psoriasis or IGA evaluations (including, but not limited to, oral or injectable corticosteroids, retinoids, 1,25-dihydroxy vitamin D3 and analogues, psoralens, sulfasalazine, hydroxyurea, fumaric acid derivatives, herbal treatments, or traditional Taiwanese, Korean, or Chinese medicines) within 4 weeks before the first administration of study drug.
19. Has used topical medications/treatments that could affect psoriasis or IGA evaluations (including, but not limited to, corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralens, pimecrolimus, tacrolimus, or topical traditional Taiwanese, Korean, or Chinese medicines) within 2 weeks before the first administration of study drug.
20. Is currently receiving lithium, antimalarials, or intramuscular gold, or has received lithium, antimalarials, or intramuscular gold within 4 weeks before the first administration of study drug.
21. Has received an experimental antibody or biologic therapy within the previous 6 months, or received any other experimental therapy or new investigational agent within 30 days or 5 half-lives (whichever is longer) of any study drug administration or is currently enrolled in another study using an investigational agent, device, or procedure.

22. Has received, or is expected to receive, any live virus or bacterial vaccination within 3 months before the first administration of study drug. For BCG vaccine, see Exclusion Criterion [23](#).
23. Has had a BCG vaccination within 12 months before screening.
24. Has known intolerance or hypersensitivity to any biologic medication, or known allergies or clinically significant reactions to murine, chimeric, or human proteins, mAbs, or antibody fragments.
25. Has known allergies, hypersensitivity, or intolerance to guselkumab or its excipients (refer to Investigator's Brochure).
26. Has a history of active granulomatous infection, including histoplasmosis or coccidioidomycosis, before screening. Refer to Inclusion Criterion [11](#) for information regarding eligibility with a history of latent TB.
27. Has a chest radiograph within 3 months before the first administration of study drug that shows an abnormality suggestive of a malignancy or current active infection, including TB.
28. Has ever had a nontuberculous mycobacterial infection or opportunistic infection (eg, cytomegalovirus, pneumocystosis, aspergillosis).
29. Has persistently indeterminate (indeterminate on repeat sampling) QuantiFERON-TB Gold test results. Indeterminate results should be handled as described in Section [9.1.2](#), Screening Phase.
30. Is infected with human immunodeficiency virus (HIV, positive serology for HIV antibody).
31. Tests positive for hepatitis B virus (HBV) infection (Attachment 2) or is seropositive for antibodies to hepatitis C virus (HCV) at screening; unless they have 2 negative HCV RNA test results 6 months apart after completing antiviral treatment and prior to screening, and have a third negative HCV RNA test result at screening.
32. Has had major surgery (eg, requiring general anesthesia and hospitalization) within 8 weeks before screening, or has not fully recovered from such surgery, or has such surgery planned during the time the subject is expected to participate in the study (40 weeks).

Note: Subjects with planned surgical procedures to be conducted under local anesthesia may participate.

33. Is known to have had a substance abuse (drug or alcohol) problem within the previous 12 months.
34. Is unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access to veins.
35. Lives in an institution on court or authority order.
36. Has any condition that, in the opinion of the investigator, would make participation not be in the best interest (eg, compromise the well-being) of the subject or that could prevent, limit, or confound the protocol-specified assessments.
37. Is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.
38. Has unstable suicidal ideation or suicidal behavior, that may be defined as an eC-SSRS rating at screening of: Suicidal ideation with intention to act (“4”), Suicidal ideation with specific plan and intent (“5”), or a suicide attempt (interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt) in the last 6 months and is confirmed to be at risk by the investigator based on an evaluation by a mental health professional. The final decision on excluding a subject will be made at the judgment of the investigator.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject’s clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 9.1.3 Screen Failure/Rescreening, describes options for retesting. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. A woman of childbearing potential who is heterosexually active must remain on a highly effective method of birth control (Inclusion Criterion 7) during the study and for at least 12 weeks after receiving the last administration of guselkumab.
2. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for at least 12 weeks after receiving the last administration of guselkumab.

3. A man who is sexually active with a woman of childbearing potential and who has not had a vasectomy must agree to use a barrier method of birth control (eg, male condom, female diaphragm or cervical cap or condom; see Inclusion Criterion 10) during the study and for at least 12 weeks after receiving the last administration of guselkumab.
4. All men must agree to not donate sperm during the study and for at least 12 weeks after receiving the last administration of guselkumab.
5. Subjects must not receive a live virus or bacterial vaccination during the study and for 3 months after the last administration of any study drug. See Prohibition 6 for information regarding BCG vaccination.
6. Subjects must not receive a BCG vaccination during the study and for 12 months after the last administration of study drug.
7. Subjects must comply with restrictions on concomitant medications and therapies during the study (Section 8).
8. Subjects must avoid prolonged sun exposure and avoid use of tanning booths or other ultraviolet light sources during the study.

5. TREATMENT ALLOCATION AND BLINDING

5.1. Procedures for Randomization and Stratification

Central randomization will be implemented in this study. At Week 0, subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared under the supervision of the sponsor. Permuted block randomization with stratification by country will be used. The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

5.2. Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

Data that may potentially unblind the treatment assignment (eg, study drug serum concentrations, antibodies to study drug, treatment allocation) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of DBL and unblinding.

Under normal circumstances, the blind should not be broken to subjects, investigators, or site monitors until the Week 40 database is locked and finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting the IWRS. It is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date of unblinding must be documented by the IWRS, in the appropriate section of the electronic case report form (eCRF), and in the source document; the reason for unblinding must be documented in the appropriate section of the eCRF and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

Subjects who have had their treatment assignment unblinded should continue to return for scheduled evaluations. The decision to continue or discontinue study treatment for these subjects will be based upon consultation of the investigator with the medical monitor.

There are 2 DBLs in this study, 1 at Week 20, and 1 at Week 40. The sponsor, with exception below, will be unblinded after the last subject has completed the Week 20 visit and the Week 20 DBL has occurred. The investigators, subjects, and sponsor site monitors will be unblinded after the last subject has completed the Week 40 visit, and the Week 40 DBL has occurred.

6. DOSAGE AND ADMINISTRATION

Subjects randomized to guselkumab will receive 100 mg of guselkumab as a 100 mg/mL solution in a single-use PFS assembled in a SelfDose device. These subjects will also receive liquid placebo for guselkumab supplied in a PFS assembled in a SelfDose device at Week 16. Subjects randomized to placebo will receive liquid placebo for guselkumab, also supplied as a PFS assembled in a SelfDose device. Subjects in the placebo group will cross over at Week 16 and receive 100 mg guselkumab as a 100 mg/mL solution in a PFS assembled in a SelfDose device. The dose regimens are as follows:

- **Group I** (n=60): guselkumab 100 mg at Weeks 0, 4, 12, 20, and 28; placebo at Week 16 to maintain the study blind.
- **Group II** (n=15): placebo at Weeks 0, 4, and 12; cross over to guselkumab 100 mg at Week 16, 20, and 28.

All study drug injections will be independently, self-administered by the subject at the study site after receiving training on the proper use of the SelfDose device. The first self-injection (Week 0) will also be observed by site staff (Section 9.3.1, Observer Assessment of Device Usability).

7. TREATMENT COMPLIANCE

Because study drug will be administered at the investigational site for all randomized subjects, treatment compliance will be controlled by site personnel.

All visits through Week 32 should occur within ± 7 days of the scheduled visit. If a study visit occurs outside this window, the sponsor should be consulted about how the subject should resume his/her normal dosing schedule relative to the baseline visit (Week 0). The Week 40 study visit should occur within +14 days of the scheduled visit.

Information regarding study drug administrations that are administered outside of the scheduled windows or missed will be recorded. Source data will be reviewed and compared with the data entries on the eCRFs to ensure accuracy. Although it is understood that treatment may be interrupted for many reasons, compliance with the treatment schedule is strongly encouraged.

SelfDose device complaints occurring during the study should be handled as instructed in Section 13, Product Quality Complaint Handling.

8. CONCOMITANT THERAPY

Concomitant therapies must be recorded throughout the study from screening and continuing until 12 weeks after the last dose of study drug for randomized subjects. Concomitant therapies should also be recorded beyond Week 40 only in conjunction with SAEs that meet the criteria outlined in Section 12.3.2, Serious Adverse Events.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements) different from the study drug, as well as all shampoos, moisturizers or emollients used to treat psoriasis, must be recorded in the eCRF. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

8.1. Concomitant Medications for Treatment of Psoriasis

8.1.1. Topical Therapy

Topical therapies that could affect psoriasis or the IGA evaluation (eg, corticosteroids, tar, anthralin, calcipotriene, tazarotene, methoxsalen, pimecrolimus, tacrolimus, or traditional Taiwanese, Korean, or Chinese medicines) are not permitted at any time during the study. The only allowable concomitant treatments for psoriasis throughout the study are shampoos (containing tar or salicylic acid only) and topical moisturizers. Subjects should not use these topical agents (shampoos, moisturizers) on the day of a study visit. Nonmedicated shampoos may be used on the day of the study visit.

8.1.2. Systemic or Phototherapy for Psoriasis

The use of systemic or phototherapy antipsoriatic medications is not permitted at any time during the study. These medications include steroids, any conventional systemic therapy that could affect psoriasis or the IGA evaluation (including but not limited to methotrexate, cyclosporine, acitretin), those targeted for reducing TNF α (including but not limited to adalimumab, infliximab, etanercept), drugs targeted for reducing IL-12, IL-17, or IL-23 (including but not limited to ustekinumab, tildrakizumab [MK3222], risankizumab [BI-655066], secukinumab

[AIN457], ixekizumab [LY2439821], or brodalumab [AMG827]), alpha-4 integrin antagonists (including but not limited to natalizumab), herbal treatments, or traditional Taiwanese, Korean, or Chinese medicines, and any other biological agent or other systemic medication that could affect psoriasis or the IGA evaluation.

8.2. Concomitant Medications for Conditions Other Than Psoriasis

Every effort should be made to keep subjects on stable concomitant medications. If the medication is temporarily discontinued because of abnormal laboratory values, side effects, concurrent illness, or the performance of a procedure, the change and reason for it should be clearly documented in the subject's medical record.

The use of stable doses of nonsteroidal anti-inflammatory drugs is allowed. However, disease-modifying agents such as methotrexate, sulfasalazine, or intramuscular gold are prohibited during the study. Antimalarial agents may not be used. Lithium may not be used.

The use of corticosteroids for indications other than psoriasis should be limited to situations for which, in the opinion of the treating physician, there are no adequate alternatives. They should be used on a short-term basis, preferably for ≤ 2 weeks. Longer-term use of corticosteroids should be discussed with the medical monitor or designee and may require discontinuation of study drug. Inhaled, otic, ocular, nasal, or other routes of mucosal delivery of corticosteroids are allowed throughout the study.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of efficacy, PK, immunogenicity, safety measurements, and usability and acceptability assessments for the SelfDose device applicable to this study.

Efficacy evaluations (ie, IGA and PASI; Section 9.2) should be completed before study drug administration at applicable visits.

Usability of the SelfDose device will be assessed by study-site personnel during a subject's first self-administered dose using the Observer Injection Checklist (Section 9.3.1). Potential device-related problems will be reported at all visits as product quality complaints (PQCs; Section 13). After each injection, study-site personnel will inspect the device to confirm that the complete dose was delivered by checking that the orange dose indicator is no longer visible and record completion of this inspection in source documents.

Acceptability of the SelfDose device by subjects will be assessed using the SIAQ (Section 9.3.2). Additional questions regarding the SelfDose device will be assessed using the SelfDose Subject Questionnaire (Section 9.3.3).

Details about who will perform and/or complete the assessments/data and the order of completion are provided in Section 9.1.4, Placebo-Controlled and Guselkumab Treatment Periods.

For females of childbearing potential, a urine pregnancy test will be performed to establish the absence of pregnancy prior to every study drug administration and at other visits as indicated on the Time and Events schedule.

The total blood volume to be collected from each subject will be approximately 142 mL. In addition, repeat or unscheduled samples may be collected for safety reasons or for technical issues with the samples.

9.1.2. Screening Phase

All subjects will have a screening visit that will occur within approximately 4 weeks prior to their Week 0 visit. The screening phase is designed to assess inclusion/exclusion criteria and establish baseline characteristics for a subject's psoriasis.

Each subject will be asked to sign the consent form at the screening visit before any study-related procedures are conducted.

The recording of AEs and concomitant medications will start after the signing of the informed consent and will continue until the last study-related procedure has been completed. The eC-SSRS ('Baseline/Screening' version) should be completed after the subject signs consent but as the first assessment by the subject before any tests, procedures, or other consultations to prevent influencing subject perceptions.

With the exception of subjects with a history of appropriately treated latent TB within 5 years of the first administration of study drug (Inclusion Criterion 11), subjects must undergo testing for TB (see Attachment 1) and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The subject should be asked about past testing for TB, including chest radiograph results and responses to tuberculin skin or other TB testing.

Subjects with a negative QuantiFERON-TB Gold test result are eligible to continue with screening procedures. Subjects with a newly identified positive QuantiFERON-TB Gold test result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB. Appropriate treatment for latent TB (ie, antituberculous drugs and duration of treatment) is defined according to local country guidelines for immunocompromised patients. If no local country guidelines for immunocompromised patients exist, United States (US) guidelines must be followed, or the subject will be excluded from the study.

A subject whose first QuantiFERON-TB Gold test result is indeterminate should have the test repeated. In the event that the second QuantiFERON-TB Gold test result is also indeterminate, the subject must be excluded from the study.

Subjects will undergo screening for HBV (see [Attachment 2](#)) and antibodies to HCV and HIV.

9.1.3. Screen Failure/Rescreening

If, during the screening phase, the subject has not met all inclusion criteria or met any exclusion criteria, or is unable or unwilling to adhere to the prohibitions and restrictions of the study, the subject is considered to be a screen failure and is not eligible to be randomized at that time.

In general, if a subject is a screen failure, but at some point in the future meets all of the subject eligibility criteria, the subject may be rescreened after a new informed consent has been obtained. Subjects who are rescreened will be assigned a new subject number, sign a new ICF, and will restart a new screening phase. Rescreening will be permitted once.

9.1.4. Placebo-Controlled and Guselkumab Treatment Periods

Week 0/Randomization

At Week 0, subjects who meet all inclusion criteria and do not demonstrate any exclusion criteria will be randomized.

Randomization visit procedures will be performed as specified in the Time and Events Schedule. The PRE self injection SIAQ (pre-SIAQ) should be completed by the subject first followed by the ‘Since Last Visit’ version of the eC-SSRS questionnaire in order to prevent influencing subject perceptions. All tests, procedures and other consultations will be performed after these questionnaires and before study agent administration (Section [9.5.1](#)).

At Week 0, if a mental health evaluation is required based on the Week 0 eC-SSRS score, either this evaluation must be conducted prior to randomization or, if not feasible, the subject should be screen-failed and then re-screened after a completed mental health evaluation, if appropriate (see Section [9.5.1](#)).

Week 4 through Week 12 (placebo-controlled period) and Week 16 through Week 32 (guselkumab treatment period)

All visit procedures will be performed as specified in the Time and Events Schedule. The ‘Since Last Visit’ version of the eC-SSRS should be completed by the subject first before any tests, procedures, or other consultations at post-baseline study visits to prevent influencing subject perceptions (Section [9.5.1](#)). All other study procedures and evaluations should be completed before the subject self-administers the study drug at each visit, except for the POST self injection SIAQ (post-SIAQ) at Weeks 4, 12, and 28 which must be completed by the subject after completion of study drug administration (Section [9.3.2](#)) and the SelfDose Subject Questionnaire which must be completed after the post-SIAQ (Section [9.3.3](#)) at Week 12.

9.1.5. Follow-Up Phase

Subjects will be followed for safety, efficacy, PK, and immunogenicity information through week 40 as indicated in the Time and Events Schedule. The ‘Since Last Visit’ version of the eC-SSRS should be completed by the subject first before any tests, procedures, or other

consultations at the follow-up visit to prevent influencing subject perceptions (Section 9.5.1). If a subject discontinues study treatment before his or her last scheduled injection, procedures described in Section 10.2, Discontinuation of Study Treatment, should be followed.

9.2. Efficacy Evaluations

Efficacy evaluations chosen for this study are consistent with those utilized to evaluate other therapies for psoriasis.

Efficacy evaluations will include the following:

- **Investigator's Global Assessment:** The IGA documents the investigator's assessment of the subject's psoriasis at a given time point (Attachment 3). Overall lesions are graded for induration, erythema, and scaling. The patient's psoriasis is assessed as cleared (0), minimal (1), mild (2), moderate (3), or severe (4).
- **Psoriasis Area and Severity Index:** The PASI is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy (Attachment 4).⁴ In the PASI system, the body is divided into 4 regions: the head, trunk, upper extremities, and lower extremities. Each of these areas is assessed separately for erythema, induration, and scaling, which are each rated on a scale of 0 to 4. The PASI produces a numeric score that can range from 0 to 72. A higher score indicates more severe disease.

Efficacy assessments will be performed at the site by an efficacy assessor trained by the sponsor and will be captured electronically in a tablet device at the appropriate visits as outlined in the Time and Events Schedule.

9.3. Usability and Acceptability Assessments

9.3.1. Observer Assessment of Device Usability

Successful, problem-free self-injection (usability) using the SelfDose device will be assessed by the completion of the Observer Injection Checklist at Week 0 (Attachment 5). Study-site personnel will observe the subject to confirm successful completion of the 3 steps, as described in the instructions for use, required to effectively and safely use the device to deliver the correct dose: (1) remove the cap, (2) position device on the injection site, and (3) inject complete dose.¹⁷ The Observer Injection Checklist will be captured electronically on a tablet device.

Study-site personnel will also report potential SelfDose device-related problems (eg, accidental needle sticks, device breakage) at all visits; any occurrences should be reported as a PQC (Section 13).

After each injection, study-site personnel will inspect the device to confirm that the complete dose was delivered by checking that the orange dose indicator is no longer visible and record completion of this inspection in source documents.

9.3.2. Self-Injection Assessment Questionnaire

Subjects will be asked to rate the acceptability of their experience using the SelfDose device with the SIAQ which was developed and validated in patients with RA.^{5,17} A paper version of the SIAQ will be used in this study.

The SIAQ (representative sample is provided in [Attachment 6](#)) includes 6 domains: feelings about injections, self-image, self-confidence, pain and skin reactions during or after the injection, ease of use of the self-injection device, and satisfaction with self-injection. Each domain is derived from one or multiple items. The subject rates each item of the SIAQ on a 5 or 6-point semantic Likert-type scale. Item scores will be transformed to obtain a score ranging from 0 (worst experience) to 10 (best experience) for each item. The domain score is the mean of the item scores included in the domain. Domain scores will be calculated only if at least half of the domain items are completed.

The PRE-self-injection module of the SIAQ includes items assessing domains of feelings about injections, self-confidence, and satisfaction with self-injection, while the POST-self-injection module of the SIAQ includes items assessing all 6 domains. In this study, the subject will complete the PRE-self-injection module before the first self-injection at Week 0, and will complete the POST-self-injection module after self-injection at Weeks 0, 4, 12, and 28.

In addition, injection site reactions may be identified in completed POST-self-injection SIAQs when a subject positively responds (all responses except “not at all”) to the questions in section “**Pain and skin reactions during or after the injection.**” These injection site reactions should be recorded on the AE page of the eCRF.

9.3.3. SelfDose Subject Questionnaire

The SelfDose Subject Questionnaire consists of 3 questions to gauge aspects of a subjects’ impression of the SelfDose device ([Attachment 7](#)). These questions are intended to supplement the SIAQ. Subjects will complete the questionnaire after all study evaluations are completed, including after they self-inject study drug and after they have completed the POST-self-injection module of the SIAQ at Week 12. Subjects will rate each question using a 5-point scale (strongly disagree, disagree, neither agree or disagree, agree, or strongly agree).

9.4. Pharmacokinetics and Immunogenicity

9.4.1. Sample Collection and Handling

Venous blood samples of approximately 7.5 mL each will be collected at the time points shown in the Time and Events Schedule for the determination of serum guselkumab concentrations and antibodies to guselkumab. A sample will also be collected at the final visit from subjects who complete or terminate study participation early. Each sample will be split into 3 aliquots (1 aliquot for serum guselkumab concentration, 1 aliquot for antibodies to guselkumab, and 1 aliquot as a back-up). Samples must be collected before study drug administration at visits when a study drug administration is scheduled. The exact dates and times of blood sample collection must be recorded in the laboratory requisition form.

Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

9.4.2. Pharmacokinetic Assessments

Serum samples will be analyzed to determine serum guselkumab concentrations using a validated, specific, and sensitive immunoassay method by the sponsor or sponsor's designee. Sponsor, or its designee, under conditions in which the subjects' identity remains blinded, will assay these samples.

9.4.3. Immunogenicity Assessments

Serum samples will be evaluated for the presence of antibodies to guselkumab using a validated assay method by the sponsor or sponsor's designee.

Serum samples that test positive for antibodies to guselkumab will be further characterized to determine if antibodies to guselkumab could neutralize the biological effects of guselkumab in vitro (ie, neutralizing antibodies [NAbs] to guselkumab).

9.5. Safety Evaluations

The safety and tolerability of study drugs (guselkumab and placebo) will be monitored by collecting information on AEs, including injection site and allergic reactions, clinical laboratory tests, physical examinations, vital sign measurements, eC-SSRS questionnaires, concomitant medication review, and early detection of TB at specified time points in the Time and Events Schedule and as described below. Serum and/or plasma samples collected for PK analyses may also be used to evaluate safety concerns that may arise during or after the study period.

Safety will be monitored through Week 40 or for 12 weeks after the last study drug administration for subjects who discontinue early. Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Any clinically important abnormalities persisting at the end of the study or at early withdrawal may be followed by the investigator until resolution or until a clinically stable endpoint is reached.

Adverse Events

Adverse events will be reported by the subject for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Early Detection of Active Tuberculosis

To aid in the early detection of TB reactivation or new TB infection during study participation, subjects must be evaluated for signs and symptoms of active TB at all scheduled visits or by telephone contact approximately every 8 to 12 weeks. The following series of questions is suggested for use during the evaluation:

- “Have you had a new cough of >14 days' duration or a change in a chronic cough?”

- “Have you had any of the following symptoms:
 - Persistent fever?
 - Unintentional weight loss?
 - Night sweats?”
- “Have you had close contact with an individual with active TB?” (If there is uncertainty as to whether a contact should be considered “close,” a physician specializing in TB should be consulted.)

If the evaluation raises suspicion that a subject may have TB reactivation or new TB infection, an immediate and thorough investigation should be undertaken, including, where possible, consultation with a physician specializing in TB.

Investigators should be aware that TB reactivation in immunocompromised subjects may present as disseminated disease or with extrapulmonary features. Subjects with evidence of active TB should be referred for appropriate treatment.

Subjects who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph, a repeat QuantiFERON-TB Gold test and, if possible, referral to a physician specializing in TB to determine the subject’s risk of developing active TB and whether treatment for latent TB is warranted.

Study drug administration should be interrupted during the investigation. A positive QuantiFERON-TB Gold test result should be considered detection of latent TB. If the QuantiFERON-TB Gold test result is indeterminate, the test should be repeated as outlined in Section 9.1.2, Screening Phase. Subjects who discontinue treatment for latent TB prematurely or who are noncompliant with therapy must immediately discontinue further administration of study drug and be encouraged to return for all subsequent scheduled study visits according to the Time and Events Schedule.

Refer to [Attachment 1](#) for details of TB testing.

Allergic Reactions

The sponsor will proactively monitor reported AEs and query the site, if necessary, to capture anaphylactic reaction/serum sickness events in the eCRF.

Injection Site Reactions

An injection site reaction is any unfavorable or unintended sign that occurs at the study drug injection site. Any adverse reaction (eg, pain, erythema, and/or induration) should be recorded on the AE page of the eCRF. See Section 9.3.2 for information regarding injection site reactions that may be identified in completed POST-self-injection SIAQs.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes

occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

All abnormal laboratory values will be evaluated for clinical significance by the investigator. If clinically significant abnormal laboratory values (in the opinion of the investigator) are detected, then the test(s) should be repeated until they return to normal or are otherwise explained by the Investigator.

Instructions for the collection, handling, and shipping of blood samples are provided in the Laboratory Manual.

The following tests will be performed by the central laboratory:

- **Hematology Panel**

-hemoglobin	-neutrophils
-hematocrit	-bands
-red blood cell (RBC) count	-eosinophils
-white blood cell (WBC) count	-basophils
-lymphocytes	-platelets
-monocytes	

- **Serum Chemistry Panel**

-sodium	-calcium
-potassium	-albumin
-chloride	-total protein
-alkaline phosphatase	-alanine aminotransferase
-urea	-total CO ₂
-creatinine	-total bilirubin
-glucose	-high-sensitivity C-reactive protein (hs-CRP)
-aspartate aminotransferase	-FSH ^a

^a Testing required for selected subjects as defined in Inclusion Criterion 7.

- **Lipids**

(Week 0 only; subjects must fast (ie, no food or beverages [except water]) for at least 8 hours before blood is drawn for lipid panel)

-total cholesterol	-total cholesterol to HDL ratio
-low density lipoprotein cholesterol (LDL)	-triglycerides
-high density lipoprotein cholesterol (HDL)	

- **Serology:** HBV, including HBV serology and HBV DNA, as appropriate (see [Attachment 2](#)) and antibodies to HCV and HIV.

Pregnancy Testing

Urine pregnancy testing is required for all women of childbearing potential at screening, before study drug administration at applicable visits, and at Week 40 or at least 12 weeks after the last study drug administration for subjects who discontinue study treatment or withdraw from the study. Pregnancy tests must be completed and negative at the study visit prior to

self-administration of study drug. All pregnancy test results must be recorded in source documents.

Physical Examination

Physical examinations will be performed by the investigator or designated physician, nurse practitioner, or physician's assistant as specified in the Time and Events Schedule. Any new, clinically significant finding (in the opinion of the investigator) must be captured as an AE (Section 12, Adverse Event Reporting). In addition, resolution of these findings during the study will be noted in the source document and in the eCRF.

Height and Weight

Height and weight will be measured at baseline (Week 0). Subjects will be instructed to remove shoes and outdoor apparel and gear prior to these measurements.

Vital Signs

Blood pressure and heart rate measurements will be assessed at the time points specified in the Time and Events Schedule.

If any clinically significant changes in vital signs are noted, they must be reported as AEs (Section 12, Adverse Event Reporting) and followed to resolution, or until reaching a clinically stable endpoint.

9.5.1. Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)

In light of the recent reports concerning suicidal ideation and behavior in patients with plaque psoriasis treated with an IL-17R antagonist (brodalumab), the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) will be used as a screening tool to prospectively evaluate the potential of guselkumab to induce suicidal ideation and behavior. The eC-SSRS defines five subtypes of suicidal ideation and behavior in addition to self-injurious behavior with no suicidal intent, and is a fully-structured, subject self-report C-SSRS questionnaire, including standardized questions, follow-up prompts, error handling routines, and scoring conventions.^{11,18} Two versions of the eC-SSRS will be used in this study, the 'Baseline/Screening' version and the 'Since Last Visit' version. The 'Baseline/Screening' version of the eC-SSRS will be conducted during the screening visit followed by the 'Since Last Visit' version of the eC-SSRS at all other visits through Week 40.

Subjects will complete the eC-SSRS questionnaire using the sponsor-provided electronic tablets. Study site personnel will train the subjects on how to use the electronic device. The eC-SSRS will be provided in the local languages in accordance with local guidelines.

The eC-SSRS will be performed during each evaluation visit according to the assessment schedule. During a visit, subjects will be directed to a private, quiet place with the electronic device to complete the assessment. Subjects who do not have suicidal behavior or ideation will answer a limited number of questions and will usually complete the assessment in about 3 minutes. Subjects with significant suicidal ideation and behavior may require up to 10 minutes to

answer all relevant questions. The eC-SSRS will be performed first at the screening visit (after signing informed consent), after the pre-SIAQ at Week 0/baseline, and before study agent administration. At all post-baseline visits, the eC-SSRS will be the first assessment/questionnaire that the subject must complete.

At the conclusion of each assessment, the site will receive an eC-SSRS Findings Report. At screening and Week 0, subjects with an eC-SSRS score greater than 0 or a response to the question of “Self-injurious behavior without suicidal intent” other than ‘NO’ must be determined to be not at risk by the investigator based on an evaluation by a mental health professional in order to be randomized. Subjects with a score on the eC-SSRS that is greater than 0 or a response to the question of “Self-injurious behavior without suicidal intent” other than ‘NO’ at any post-baseline visit will also be referred to an appropriate mental health professional for evaluation. If a subject’s psychiatric disorder can be adequately treated with psychotherapy and/or pharmacotherapy then the subject, at the discretion of the investigator, should be continued with treatment. Ultimately, the determination of suicidality and risk is up to the investigator’s clinical judgment following evaluation by a mental health professional (eg, psychiatrist, psychologist, or appropriately trained social worker or nurse).

Positive reports are generated from the eC-SSRS vendor for ANY of the following findings:

- Suicidal ideation with intention to act (“4”)
- Suicidal ideation with specific plan and intent (“5”)
- Made suicide attempt
- Interrupted suicide attempt
- Aborted suicide attempt
- Preparatory behaviors for making a suicide attempt.

Negative suicidality indication reports are generated from the eC-SSRS vendor when there are NO indications of the above.

The subject should not be released from the site until the eC-SSRS Findings Report (both for negative and positive reports) is reviewed by the investigator and the subject’s risk has been assessed and follow-up determined, as appropriate.

For each score, the following actions and associated alerts will be generated, if applicable:

- Score of 0: No further action is needed.
- Score > 0: Subject risk assessed and referral to a mental health professional.
 - Score of 1, 2, or 3: Negative findings report will be generated.

- Score of 4 or higher: Positive findings report will be generated. When the system reports that the subject has a positive suicidal indication (including for an incomplete assessment), the site will be immediately notified by fax/email and a telephone call from the eC-SSRS vendor.
- Self-injurious behavior without suicidal intent = YES or ‘Question Mark (ambiguous response)’: Subject risk assessed and referral to a mental health professional. Negative findings report will be generated.

Interruption or the discontinuation of study treatment should be considered for any subject who reports suicidal ideation with intention to act (“4”), suicidal ideation with specific plan and intent (“5”), or a suicide attempt (interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt) on a post-baseline eC-SSRS assessment and who is deemed to be at risk by the investigator based upon evaluation by a mental health professional. Discussion of such subjects with the medical monitor or designee is required (See Section 10.2). The final decision on suitability for continuing in the study will be made by the investigator.

Any eC-SSRS finding, which in the opinion of the investigator is new or considered to be a worsening and clinically significant, should be reported on the AE eCRF (see Section 12).

9.6. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the laboratory requisition form.

Refer to the Time and Events Schedule for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the Laboratory Manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the Laboratory Manual.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered to have completed the study if he or she has completed assessments at Week 40 of the study. Subjects who prematurely discontinued study treatment for any reason before completion of the study will not be considered to have completed the study.

10.2. Discontinuation of Study Treatment

If a subject’s study treatment must be discontinued before the end of the treatment regimen, it will not result in automatic withdrawal of the subject from the study.

A subject's study treatment should be discontinued if:

- The investigator believes that for safety reasons (eg, AE) it is in the best interest of the subject to discontinue study treatment.
- The subject becomes pregnant.
- The subject is diagnosed with a malignancy, with the exception of no more than 2 localized basal cell skin cancers that are treated with no evidence of recurrence or residual disease.
- The subject is deemed ineligible according to the following TB screening criteria:
 - A diagnosis of active TB is made.
 - A subject has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination, or has had recent close contact with a person with active TB, and cannot or will not continue to undergo additional evaluation.
 - A subject undergoing evaluation has a chest radiograph with evidence of current active TB and/or a positive QuantiFERON-TB Gold test result, unless active TB can be ruled out and appropriate treatment for latent TB can be initiated before the next administration of study drug and continued to completion. Indeterminate QuantiFERON-TB Gold test results should be handled as described in Section 9.1.2, Screening Phase.
 - A subject receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.
- The subject initiates a protocol-prohibited medication, eg, for a worsening of his or her psoriasis (unless agreed to by the medical monitor).
- The subject withdraws consent for administration of study drug.
- The subject is unable to adhere to the study visit schedule or comply with protocol requirements.
- The subject develops an allergic reaction such as bronchospasm with wheezing and/or dyspnea requiring ventilatory support, or symptomatic hypotension that occurs following a study drug administration.
- The subject has a reaction resulting in myalgia and/or arthralgia with fever and/or rash (suggestive of serum sickness and not representative of signs and symptoms of other recognized clinical syndromes) occurring 1 to 14 days after an injection of study drug. These may be accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache.
- Discontinuation of study treatment should be considered for subjects who report suicidal ideation with intention to act ("4"), suicidal ideation with specific plan and intent ("5"), or a suicide attempt (interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt) on a post-baseline eC-SSRS assessment. Discussion of such subjects with the medical monitor or designee is required.
- Discontinuation of study treatment should be considered for subjects who develop a serious or opportunistic infection. Discussion of such subjects with the medical monitor or designee

should also be considered. The final decision on suitability for continuing with study agent will be made by the investigator, based upon evaluation by a mental health professional.

If a subject discontinues study treatment before his or her last scheduled injection, he or she should return for the remaining regularly scheduled study visits for at least 12 weeks after receiving the last administration of study drug. For subjects who complete their final study visit prior to Week 40, every effort should be made to conduct the Week 40 assessments as indicated in the Time and Events Schedule; serum samples for PK and immunogenicity assessments should also be collected at that final visit.

Subjects who decide to discontinue study drug administration must be interviewed by the investigator to determine if a specific reason for discontinuing study drug can be identified. Subjects should be explicitly asked about the possible contribution of AEs to their decision to discontinue study drug; investigators should confirm that any AE information elicited has been documented. If a subject elects to discontinue study drug due to an AE, the event should be recorded as the reason for study drug discontinuation, even if the investigator's assessment is that the AE would not require study drug discontinuation. The reason for study drug discontinuation must be documented in the eCRF and in source documents. Study drug assigned to a subject who discontinues may not be assigned to another subject.

10.3. Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death

To ensure access for subject follow-up, study sites should try to obtain both primary and secondary telephone contact numbers from subjects (eg, home, work, and mobile phones), as well as other contact information such as email addresses, and emphasize the importance of follow-up information to the subject, before randomization.

For subjects who withdraw from study participation, every effort should be made to conduct the Week 40 assessments, as indicated in the Time and Events Schedule.

If a subject fails to return for study visits, study site personnel must make all reasonable efforts to contact the subject to determine the subject's reason for discontinuation/withdrawal before considering the subject to be lost to follow-up. Such efforts should include repeated telephone calls, certified letters, email requests, etc. Measures taken to obtain follow-up information must be documented.

Withdrawal of consent should be a very unusual occurrence in a clinical trial; the investigator should make every effort to maintain good subject relationships to avoid withdrawals of consent. For subjects who truly request withdrawal of consent, it is recommended that the subject withdraw consent in writing; if the subject or the subject's representative refuses to do so or is

physically unavailable, the study site should document the reason for the subject's failure to withdraw consent in writing, sign the documentation, and maintain it with the subject's source records.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw from the study will not be replaced.

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

Descriptive statistics will include counts and proportions for categorical data, and median, mean, interquartile range, and range for continuous data. Graphical data displays may also be used to summarize the data.

The Fisher's exact test will be used to compare the proportion of subjects responding to treatment. Continuous response parameters will be compared using an analysis of variance model, with country as a covariate. All statistical testing will be performed 2-sided.

11.1. Subject Information

Subjects will be included in the efficacy analyses according to their assigned treatment group regardless of whether or not they received the assignment treatment. For the primary efficacy analysis, data from all randomized and treated subjects will be analyzed. The treated population, which includes all randomized subjects who receive at least 1 dose (complete or partial) of study drug, will be used for the PK, immunogenicity, and safety analyses; subjects will be included according to the actual treatment received.

Descriptive statistics by the randomized treatment group based on all randomized and treated subjects will be provided for subject dispositions, demographics, baseline disease characteristics, and prior and concomitant medications. The baseline measurement is defined as the closest measurement taken before or at Week 0.

11.2. Sample Size Determination

This study is designed to evaluate the efficacy of guselkumab vs placebo using the SelfDose device.

The assumptions for the sample size and power calculations are based on the data from the guselkumab CNT01959PSO2001 study:

- The proportion of placebo subjects who achieved an IGA score of cleared (0) or minimal (1) and a PASI 90 response was 10% and 5%, respectively. Note PGA was used in CNT01959PSO2001. PGA is a similar measure to IGA which will be used in this study.
- The proportion of subjects who achieved an IGA score of cleared (0) or minimal (1) response at Week 16 was 86% in the guselkumab 100 mg group.
- The proportion of subjects who achieved a PASI 90 response at Week 16 was 62% in the guselkumab 100 mg group.

As shown in the [Table 1](#) below, based on the above assumptions, with a total of approximately 75 subjects randomized in a 4:1 ratio to guselkumab 100 mg (n=60) and placebo (n=15), there will be at least 99% power to detect differences for both co-primary endpoints in the proportion of subjects achieving an IGA score of cleared (0) or minimal (1) and the proportion of subjects who achieve a PASI 90 response between the placebo and guselkumab groups at Week 16, at a significance level of 0.05. This sample size was also chosen to provide adequate power for major secondary endpoints.

Table 2: Power to Detect a Treatment Effect Based on Different Proportions of Subjects Achieving the Co primary Endpoints

Co-primary Endpoints		Power
IGA cleared (0) or minimal (1) response at Week 16		
<u>Placebo</u> (n=15)	<u>Guselkumab 100 mg q8w</u> (n=60)	
10%	70%	>99%
	75%	>99%
	80%	>99%
PASI 90 response at Week 16		
<u>Placebo</u> (n=15)	<u>Guselkumab 100 mg q8w</u> (n=60)	
5%	55%	99%
	60%	>99%
	65%	>99%

IGA=Investigator's Global Assessment; PASI=Psoriasis Area and Severity Index; q8w=every 8 weeks.

11.3. Interim Analysis

No formal interim analyses will be performed.

11.4. Efficacy Analysis

11.4.1. Analysis Data Set

For the primary analysis and major secondary analyses, all randomized and treated subjects will be included. For all efficacy analyses, subjects will be analyzed according to the treatment group to which they were randomized, regardless of the treatment they actually received.

11.4.2. Primary Analysis

The 2 co-primary endpoints (Section 2.1.2) will be compared between the guselkumab group and the placebo group. Subjects who meet treatment failure criteria (Section 11.6), Criteria for Endpoints, before Week 16 will be considered nonresponders for the co-primary endpoints at Week 16. In addition, subjects who do not return for evaluation at Week 16 will be considered nonresponders at Week 16.

The analysis will be performed using a Fisher's exact test, 2-sided ($\alpha=0.05$).

11.4.3. Major Secondary Analyses

The major secondary endpoints (Section 2.1.2) will be compared between the guselkumab group and the placebo group. The analyses will be performed using a Fisher's exact test, 2-sided ($\alpha=0.05$).

In order to control the overall Type 1 error rate, the primary analysis and major secondary analyses will be tested in a fixed sequence. That is, the first major secondary endpoint will be tested only if the co-primary endpoints are positive. Similarly, the second major secondary endpoint will be tested only if the first major secondary endpoint is positive.

11.4.4. Other Efficacy Analyses

Efficacy endpoints (Section 2.1.2) will be compared between the guselkumab group and the placebo group and nominal p-values will be provided. The efficacy endpoints will also be summarized over time through Week 16, and from Week 16 through Week 40.

Furthermore, subgroup analyses will be performed to evaluate consistency of the co-primary endpoints over demographics, baseline disease characteristics, and prior medications. Additional efficacy analyses may be performed and will be documented in the SAP.

11.5. Usability and Acceptability Assessments

Endpoints related to usability and acceptability (Section 2.1.2) will be summarized by treatment group and for the overall population.

Ratings for the SelfDose Subject Questionnaire will be summarized at Week 12 by question, by treatment group, and for the overall population.

11.6. Criteria for Endpoints

Treatment Failure: Subjects who discontinue study treatment due to lack of efficacy or an AE of worsening of psoriasis, or who started a protocol-prohibited medication/therapy during the study that could improve psoriasis are considered treatment failures. The treatment failure rules will be documented in detail in the SAP.

PASI 50 Responders: Subjects with $\geq 50\%$ improvement in PASI from baseline.

PASI 75 Responders: Subjects with $\geq 75\%$ improvement in PASI from baseline.

PASI 90 Responders: Subjects with $\geq 90\%$ improvement in PASI from baseline.

PASI 100 Responders: Subjects with 100% improvement in PASI from baseline.

11.7. Pharmacokinetic Analyses

Serum guselkumab concentrations over time will be summarized by treatment group. Descriptive statistics, including arithmetic mean, standard deviation, median, interquartile range, minimum, and maximum will be calculated at each sampling time point. All concentrations below the lowest quantifiable sample concentration of the assay (BQL) or missing data will be labeled as such in the concentration data listing or statistical analysis system (SAS[®]) dataset. The BQL concentrations will be treated as zero in the summary statistics.

11.8. Immunogenicity Analyses

The incidence and titers of antibodies to guselkumab will be summarized for all subjects who receive at least 1 dose of guselkumab and have appropriate samples for detection of antibodies to guselkumab (ie, subjects with at least 1 sample obtained after their first dose of guselkumab). A listing of subjects who are positive for antibodies to guselkumab will be provided.

The incidence of NAbs to guselkumab will be summarized for subjects who are positive for antibodies to guselkumab and have samples evaluable for NAbs.

11.9. Safety Analyses

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs with onset during the treatment phase (ie, treatment-emergent AEs and AEs that have worsened since baseline) will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

Summaries, listings, and/or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience a severe or a serious AE.

The following analyses will also be used to assess the safety of subjects in the study:

- The incidence and type of AEs.
- The incidence and type of SAEs.
- The incidence and type of infections.
- The incidence and type of reasonably related AEs.
- The incidence and type of injection site reactions.
- The laboratory parameters and change from baseline in laboratory parameters (hematology and chemistry).
- National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grades will be used in the summary of select hematology and chemistry parameters. A listing of subjects with post-baseline abnormal laboratory results based on NCI-CTCAE grades will also be provided.

Vital Signs

Descriptive statistics of heart rate and blood pressure (systolic and diastolic) values and changes from baseline will be summarized by treatment group.

Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)

Suicide-related thoughts and behaviors based on the eC-SSRS will be summarized descriptively by treatment group.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last AE recording).

Serious Adverse Event

An SAE based on ICH and European Union (EU) Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
(The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For guselkumab, the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure.

Adverse Event Associated With the Use of the Drug

An AE is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2, Attribute Definitions.

12.1.2. Attribution Definitions**Not Related**

An AE that is not related to the use of the drug.

Doubtful

An AE for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An AE that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An AE that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)

Any special reporting situation that also meets the criteria of an SAE should be recorded on the SAE page of the eCRF. Refer to Section [12.3.2](#), Serious Adverse Events, for information on reporting SAEs.

12.3. Procedures

12.3.1. All Adverse Events

All AEs and special reporting situations (Section [12.2](#)), whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety). Serious AEs, including those spontaneously reported to the investigator within 12 weeks after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol. Anticipated events will be recorded and reported as described in [Attachment 8](#).

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

Serious AEs relating to lack of efficacy (eg, events attributed to “psoriasis”) or progression of the disease under study will not be individually unblinded for expedited reporting. These anticipated events will be recorded and reported as described in [Attachment 8](#).

All SAEs and nonserious AEs that represent any of the following diagnoses or any symptoms associated with the following diagnoses (eg, chest pain, dizziness) must be reported to the sponsor and will require efforts to obtain additional medical records:

- myocardial infarction
- stroke
- cardiovascular death
- unstable angina
- coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery)
- transient ischemic attack
- venous and peripheral arterial vascular thrombotic events (ie, deep vein thrombosis and pulmonary embolism)
- congestive heart failure
- cardiac arrhythmia
- syncope of a cardiovascular origin
- severe/accelerated hypertension leading to hospitalization

If the event is an SAE, the procedures outlined in Section [12.3.2](#), Serious Adverse Events, should be followed. If the event is a nonserious AE, procedures outlined in the Trial Center File for nonserious AEs (as described above) should be followed.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a “wallet (study) card” and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator’s name and 24-hour contact telephone number
- Local sponsor’s name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax) or electronic mail.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject’s participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE.

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject’s participation in a study must be reported as an SAE, except hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility).

The cause of death of a subject in a study within 12 weeks of the last dose of study drug, whether or not the event is expected or associated with the study drug, is considered an SAE.

12.3.3. Pregnancy

All initial reports of pregnancy must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, stillbirth, and congenital anomaly) are considered SAEs and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.3.4. Events of Special Interest

Any newly identified malignancy or case of active TB occurring after the first administration of study drug in subjects participating in this clinical study must be reported by the investigator according to the procedures in Section 12.3.2, Serious Adverse Events. Investigators are also advised that active TB is considered a reportable disease in most countries. These events are to be considered serious only if they meet the definition of an SAE.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A PQC is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event. All PQCs will be documented in source documents and the eCRF.

If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.3.2, Serious Adverse Events) and complete both the PQC and SAE reporting forms. A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drugs

The guselkumab PFS supplied for this study is a single-use sterile solution in a 1-mL glass syringe with a 27 gauge, 1/2 inch fixed needle assembled with a facilitated injection device (referred to as the SelfDose device). Each single-use SelfDose device contains 100 mg/mL of guselkumab in 1 mL syringe volume. No preservatives are present. The guselkumab solution should be essentially free of visible particulate matter. SelfDose device is manually operated, disposable, and intended to deliver the contents of the PFS for SC injection. The SelfDose device incorporates a needle guard that automatically shields the needle after complete injection of the PFS contents. Guselkumab will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

Placebo for guselkumab is supplied as a single-use sterile solution in a SelfDose device, as described above. Each single-use placebo SelfDose device contains a 1 mL syringe volume of placebo.

14.2. Packaging

The study drug will be packaged in individual subject kits. The investigational supplies will be uniquely packaged to assure that they are appropriately managed throughout the supply chain process.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Handling, and Storage

All study drug must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C) and protected from light. Vigorous shaking of the product should be avoided. The sterile product does not contain preservatives and is designed for single use only. Protection from light is not required during administration.

Further details regarding the handling and storage of guselkumab and placebo will be provided in the Site Investigational Product Procedures Manual.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject must be documented on the drug accountability form. All study drugs will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes. The immediate destruction of these drug supplies should be documented in the drug accountability records on site.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator Brochure for guselkumab
- Site Investigational Product Procedures Manual
- Laboratory Manual
- Laboratory kits
- Self-Dose practice device, associated instructions for use, and training materials
- Interactive web response system manual
- Electronic data capture (eDC) manual
- Electronic tablet device and user manual
- Self-Injection Assessment Questionnaire
- Electronic Columbia-Suicide Severity Rating Scale
- Observer Injection Checklist
- SelfDose Subject Questionnaire
- Sample ICF
- Recruitment materials as needed

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population of this study based on the standard of the American Red Cross (1 pint/473 mL of blood for donation).

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed and subsequent disease-related treatments or to obtain information about his or her survival status.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory PK and immunogenicity research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand guselkumab, to understand psoriasis, to understand differential drug responders, and to develop tests/assays related to guselkumab and psoriasis. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3, Withdrawal From the Study, Withdrawal From the Use of Samples in Future Research).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documentation must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

Investigator-completed efficacy evaluations (IGA, PASI), the Observer Injection Checklist, and the subject-completed eC-SSRS will be recorded directly into an electronic tablet device during the visit at the study site. These data will be considered electronic source documentation.

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

17.5. Case Report Form Completion

Case report forms are provided for each subject in electronic format.

Electronic data capture will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an electronic eCRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the eCRF.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study, with the exception of the investigator-reported efficacy evaluations (IGA, PASI) and the Observer Injection Checklist that will be entered directly into an electronic tablet device as electronic source documentation, must be recorded in eCRFs prepared by the sponsor. Data must be entered into eCRFs in English. Study site personnel must complete the eCRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible. The investigator must verify that all data entries in the eCRFs are accurate and correct.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or study-site personnel must adjust the eCRF (if applicable) and complete the query.

If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

- Study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Study site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager can generate a query for resolution by the study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, direct transmission of clinical laboratory data from a central laboratory, and direct transmission of efficacy data, eC-SSR questionnaires, and the Observer Injection Checklist to the vendor database and then to the sponsor's database. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed with the last visit for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject visit at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding guselkumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of guselkumab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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ATTACHMENT 1: QUANTI-FERON®-TB GOLD TESTING

The QuantiFERON®-TB Gold test is one of the interferon- γ (IFN- γ) based blood assays for TB screening (Cellestis, 2009). It utilizes the recently identified *M. tuberculosis*-specific antigens ESAT-6 and CFP-10 in the standard format, as well as TB7.7 (p4) in the In-Tube format, to detect in vitro cell-mediated immune responses in infected individuals. The QuantiFERON®-TB Gold assay measures the amount of IFN- γ produced by sensitized T-cells when stimulated with the synthetic *M. tuberculosis*-specific antigens. In *M. tuberculosis*-infected persons, sensitized T lymphocytes will secrete IFN- γ in response to stimulation with the *M. tuberculosis*-specific antigens and, thus, the QuantiFERON®-TB Gold test should be positive. Because the antigens used in the test are specific to *M. tuberculosis* and not found in BCG, the test is not confounded by BCG vaccination, unlike the tuberculin skin test. However, there is some cross-reactivity with the 3 Mycobacterium species, *M. kansasii*, *M. marinum*, and *M. szulgai*. Thus, a positive test could be the result of infection with one of these 3 species of Mycobacterium, in the absence of *M. tuberculosis* infection.

In a study of the QuantiFERON®-TB Gold test (standard format) in subjects with active TB, sensitivity has been shown to be approximately 89% (Mori et al, 2004). Specificity of the test in healthy BCG-vaccinated individuals has been demonstrated to be more than 98%. In contrast, the sensitivity and specificity of the tuberculin skin test was noted to be only about 66% and 35% in a study of Japanese patients with active TB and healthy BCG-vaccinated young adults, respectively. However, sensitivity and specificity of the tuberculin skin test depend on the population being studied, and the tuberculin skin test performs best in healthy young adults who have not been BCG-vaccinated.

Data from a limited number of published studies examining the performance of the QuantiFERON®-TB Gold assay in immunosuppressed populations suggest that the sensitivity of the QuantiFERON®-TB Gold test is better than the tuberculin skin test even in immunosuppressed patients (Ferrara et al, 2005; Kobashi et al, 2007; Matulis et al, 2008). The ability of IFN- γ -based tests to detect latent infection has been more difficult to study due to the lack of a gold standard diagnostic test; however, several TB outbreak studies have demonstrated that the tests correlated better than the tuberculin skin test with the degree of exposure that contacts had to the index TB case (Brock et al, 2004; Ewer et al, 2003). In addition, TB contact tracing studies have shown that patients who had a positive QuantiFERON®-TB Gold test result and were not treated for latent TB infection were much more likely to develop active TB during longitudinal follow-up than those who had a positive tuberculin skin test and a negative QuantiFERON®-TB Gold test result (Higuchi et al, 2007; Diel et al, 2008).

Although the performance of the new IFN- γ -based blood tests for active or latent *M. tuberculosis* infection have not been well validated in the immunosuppressed population, experts believe these new tests will be at least as, if not more, sensitive, and definitely more specific, than the tuberculin skin test (Barnes, 2004; personal communication, April, 2008 TB Advisory Board).

Performing the QuantiFERON®-TB Gold Test

The QuantiFERON®-TB Gold test In-Tube format will be provided for this study. The In-Tube format contains 1 additional *M. tuberculosis*-specific antigen, TB7.7 (p4), which is thought to increase the specificity of the test.

To perform the test using the In-Tube format, blood is drawn through standard venipuncture into supplied tubes that already contain the *M. tuberculosis*-specific antigens. Approximately 3 tubes will be needed per subject, each requiring 1 mL of blood. One tube contains the *M. tuberculosis*-specific antigens, while the remaining tubes contain positive and negative control reagents. Thorough mixing of the blood with the antigens is necessary prior to incubation. The blood is then incubated for 16 to 24 hours at 37°C, after which tubes are centrifuged for approximately 15 minutes at 2000 to 3000 g. Following centrifugation, plasma is harvested from each tube, frozen, and shipped on dry ice to the central laboratory. The central laboratory will perform an ELISA to quantify the amount of IFN- γ present in the plasma using spectrophotometry and computer software analysis.

The central laboratory will analyze and report results for each subject, and sites will be informed of the results. Subjects who have an indeterminate result should have the test repeated.

Adherence to Local Guidelines

Local country guidelines **for immunocompromised patients** should be consulted for acceptable antituberculous treatment regimens for latent TB. If no local country guidelines for immunocompromised patients exist, United States (US) guidelines must be followed.

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ATTACHMENT 2: HEPATITIS B VIRUS (HBV) SCREENING WITH HBV DNA TESTING

Subjects must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total):

- Subjects who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) **are eligible** for this study.
- Subjects who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti-HBc+) **and** surface antibody (anti-HBs+) **are eligible** for this study.
- Subjects who test **positive only** for **surface antibody** (anti-HBs+) **are eligible** for this study.
- Subjects who test **positive** for surface antigen (HBsAg+) **are NOT eligible** for this study, regardless of the results of other hepatitis B tests.
- Subjects who test **positive only** for **core antibody** (anti-HBc+) must undergo further testing for the presence of hepatitis B virus deoxyribonucleic acid (HBV DNA test). If the HBV DNA test is **positive**, the subject **is NOT eligible** for this study. If the HBV DNA test is **negative**, the subject **is eligible** for this study. In the event the HBV DNA test cannot be performed, the subject **is NOT eligible** for this study.

For subjects who **are not eligible for this study due to HBV test results**, consultation with a physician with expertise in the treatment of hepatitis B virus infection is recommended.

Eligibility based on hepatitis B virus test results			
Action	Hepatitis B test result		
	Hepatitis B surface antigen (HBsAg)	Hepatitis B surface antibody (anti-HBs)	Hepatitis B core antibody (anti-HBc total)
Include	—	—	—
	—	+	—
	—	+	+
Exclude	+	— or +	— or +
Require testing for presence HBV DNA ^a	—	—	+
a If HBV DNA is detectable, exclude from the clinical study. If HBV DNA testing cannot be performed, or there is evidence of chronic liver disease, exclude from the clinical study.			

ATTACHMENT 3: INVESTIGATOR'S GLOBAL ASSESSMENT

Induration (I) (averaged over all lesions; use the National Psoriasis Foundation Reference card for measurement)

- 0 = no evidence of plaque elevation
- 1 = minimal plaque elevation, = 0.25 mm
- 2 = mild plaque elevation, = 0.5 mm
- 3 = moderate plaque elevation, = 0.75 mm
- 4 = severe plaque elevation, > 1 mm

Erythema (E) (averaged over all lesions)

- 0 = no evidence of erythema, hyperpigmentation may be present
- 1 = faint erythema
- 2 = light red coloration
- 3 = moderate red coloration
- 4 = bright red coloration

Scaling (S) (averaged over all lesions)

- 0 = no evidence of scaling
- 1 = minimal; occasional fine scale over less than 5% of the lesion
- 2 = mild; fine scale dominates
- 3 = moderate; coarse scale predominates
- 4 = severe; thick, scale predominates

Total Average = $(I + E + S) / 3$

Investigator's Global Assessment based upon above Total Average

- 0 = Cleared, except for residual discoloration
 - 1 = Minimal - majority of lesions have individual scores for $I + E + S / 3$ that averages 1
 - 2 = Mild - majority of lesions have individual scores for $I + E + S / 3$ that averages 2
 - 3 = Moderate - majority of lesions have individual scores for $I + E + S / 3$ that averages 3
 - 4 = Severe - majority of lesions have individual scores for $I + E + S / 3$ that averages 4
- Note: Scores should be rounded to the nearest whole number. If total ≤ 1.49 , score = 1; if total ≥ 1.50 , score = 2.

ATTACHMENT 4: PSORIASIS AREA AND SEVERITY INDEX

The Psoriasis Area and Severity Index (PASI) is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy. The PASI produces a numeric score that can range from 0 to 72. The severity of the disease is calculated as follows.

In the PASI system, the body is divided into 4 regions: the head (h), trunk (t), upper extremities (u), and lower extremities (l), which account for 10%, 30%, 20%, and 40% of the total body surface area, respectively. Each of these areas is assessed separately for erythema, induration and scaling, which are each rated on a scale of 0 to 4.

The scoring system for the signs of the disease (erythema, induration, and scaling) is: 0 = none, 1 = slight, 2 = moderate, 3 = severe, and 4 = very severe.

The scale for estimating the area of involvement for psoriatic lesions is outlined below.

- 0 = no involvement
- 1 = 1% to 9% involvement
- 2 = 10% to 29% involvement
- 3 = 30% to 49% involvement
- 4 = 50% to 69% involvement
- 5 = 70% to 89% involvement
- 6 = 90% to 100% involvement

To help with the area assessments, the following conventions should be noted:

- a. The neck is considered part of the head
- b. The axillae and groin are part of the trunk
- c. The buttocks are part of the lower extremities

The PASI formula is:

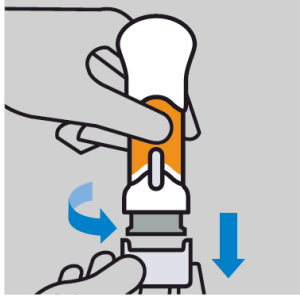
$$\text{PASI} = 0.1 (\text{Eh} + \text{Ih} + \text{Sh}) \text{Ah} + 0.3 (\text{Et} + \text{It} + \text{St}) \text{At} + 0.2 (\text{Eu} + \text{Iu} + \text{Su}) \text{Au} + 0.4 (\text{El} + \text{Il} + \text{Sl}) \text{Al}$$

Where E = erythema, I = induration, S = scaling, and A = area

ATTACHMENT 5: OBSERVER INJECTION CHECKLIST

This form is intended to be completed to determine if the WEEK 0 dose was delivered successfully BY THE SUBJECT and should be completed by the study staff observing the injections.

Subject Number _____

Step 1: Remove Cap

Did subject successfully remove cap*?

Yes ☐ No ☐

If No,

a. did they understand that they needed to remove the cap?

Yes ☐ No ☐

b. were they physically able to remove the cap

Yes ☐ No ☐

*Note: if the subject attempts to inject without removing the cap, and self-corrects their own action, this is not considered a failure and the response to this question should be YES.

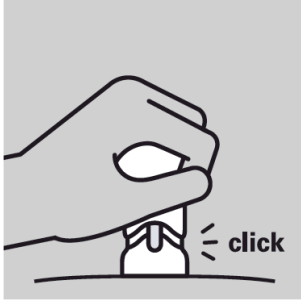
Step 2: Position Device on Injection Site

Did the subject select the correct injection site?

Yes ☐ No ☐

Did the subject position the device at approximately a 90 degree angle on the injection site?

Yes ☐ No ☐

Step 3: Inject Complete Dose

Did the subject push the handle all the way down so the orange dose indicator disappeared completely?

Yes ☐ No ☐

Note: check device to ensure orange dose indicator is not visible.

Were there any device-related problems associated with this injection?

Yes ☐ No ☐

If Yes, please follow procedures for reporting a product quality complaint (PQC).

ATTACHMENT 6: SELF-INJECTION ASSESSMENT QUESTIONNAIRE**SELF-INJECTION ASSESSMENT QUESTIONNAIRE (SIAQ)****- PRE-Self-Injection -****INTRODUCTION**

The following questions ask about injections in general and your feelings about giving yourself an injection.

Thank you for completing this questionnaire by yourself, preferably in a quiet environment. Take as much time as you need to complete it. There are no right or wrong answers. Your answers will remain strictly confidential and anonymous.

Please answer each question below by checking the box that best represents your opinion
(Check only one box per question).

1. In general, how afraid are you of needles?

Not at all <input type="checkbox"/>	A little <input type="checkbox"/>	Moderately <input type="checkbox"/>	Very <input type="checkbox"/>	Extremely <input type="checkbox"/>
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2. In general, how afraid are you of having an injection?

Not at all <input type="checkbox"/>	A little <input type="checkbox"/>	Moderately <input type="checkbox"/>	Very <input type="checkbox"/>	Extremely <input type="checkbox"/>
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3. How anxious do you feel about giving **yourself** an injection?

Not at all <input type="checkbox"/>	A little <input type="checkbox"/>	Moderately <input type="checkbox"/>	Very <input type="checkbox"/>	Extremely <input type="checkbox"/>
--	--------------------------------------	--	----------------------------------	---------------------------------------

4. How confident are you about giving yourself an injection in **the right way**?

Not at all <input type="checkbox"/>	A little <input type="checkbox"/>	Moderately <input type="checkbox"/>	Very <input type="checkbox"/>	Extremely <input type="checkbox"/>
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5. How confident are you about giving yourself an injection in a **clean and sterile way**?

Not at all <input type="checkbox"/>	A little <input type="checkbox"/>	Moderately <input type="checkbox"/>	Very <input type="checkbox"/>	Extremely <input type="checkbox"/>
--	--------------------------------------	--	----------------------------------	---------------------------------------

6. How confident are you about giving yourself an injection **safely**?

Not at all <input type="checkbox"/>	A little <input type="checkbox"/>	Moderately <input type="checkbox"/>	Very <input type="checkbox"/>	Extremely <input type="checkbox"/>
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7. Overall, how satisfied are you with your current way of taking your medication?

Very dissatisfied <input type="checkbox"/>	Dissatisfied <input type="checkbox"/>	Neither dissatisfied nor satisfied <input type="checkbox"/>	Satisfied <input type="checkbox"/>	Very satisfied <input type="checkbox"/>
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Thank you for completing this questionnaire

SELF-INJECTION ASSESSMENT QUESTIONNAIRE (SIAQ)**- POST-Self-Injection -****INTRODUCTION**

The following questions concern the self-injection of your medication and must be answered after giving yourself an injection.

Thank you for completing this questionnaire by yourself, preferably in a quiet environment. Take as much time as you need to complete it. There are no right or wrong answers. Your answers will remain strictly confidential and anonymous.

FEELINGS ABOUT INJECTIONS

The following questions concern your **feelings about injections**.

Please answer each question below by checking the box that best represents your opinion
(Check only one box per question).

In general, how afraid are you of needles?

Not at all	A little	Moderately	Very	Extremely
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

In general, how afraid are you of having an injection?

Not at all	A little	Moderately	Very	Extremely
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

How anxious do you feel about giving **yourself** an injection?

Not at all	A little	Moderately	Very	Extremely
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

SELF-IMAGE

The following question concerns your **self-image**.

Please answer the question below by checking the box that best represents your opinion
(Check only one box).

How embarrassed would you feel if someone saw you with the self-injection device?

Not at all	A little	Moderately	Very	Extremely
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

SELF-CONFIDENCE

The following questions concern your **confidence** about giving yourself an injection.

Please answer each question below by checking the box that best represents your opinion
(Check only one box per question).

How confident are you about giving yourself an injection in **the right way**?

Not at all	A little	Moderately	Very	Extremely
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

How confident are you about giving yourself an injection in a **clean and sterile way**?

Not at all	A little	Moderately	Very	Extremely
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

How confident are you about giving yourself an injection **safely**?

Not at all	A little	Moderately	Very	Extremely
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

PAIN AND SKIN REACTIONS DURING OR AFTER THE INJECTION
--

The following questions ask about **pain and skin reactions** you may have experienced during or after the injection.

Please answer each question below by checking the box that best represents your opinion
(Check only one box per question).

During and/or after the injection, how bothered were you by:	Not at all	A little	Moderately	Very	Extremely
a. pain ?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. burning sensation ?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. cold sensation ?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

During and/or after the injection, how bothered were you by:	Not at all	A little	Moderately	Very	Extremely
a. itching at the injection site?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. redness at the injection site?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. swelling at the injection site?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. bruising at the injection site?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
e. hardening at the injection site?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

EASE OF USE OF THE SELF-INJECTION DEVICE

The following questions ask about the **ease of use** of the self-injection device.

Please answer each question below by checking the box that best represents your opinion
(Check only one box per question).

How difficult or easy was it to:	Very difficult	Difficult	Somewhat difficult	Somewhat easy	Easy	Very easy
remove the cap?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
depress the plunger or button on the device?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
administer the injection without any help?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
use the self-injection device?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

How does the device fit in your hand?

Very uncomfortably	Uncomfortably	Somewhat uncomfortably	Somewhat comfortably	Comfortably	Very comfortably
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

SATISFACTION WITH SELF-INJECTION

The following questions ask about your **satisfaction** with self-injection.

Please answer each question below by checking the box that best represents your opinion
(Check only one box per question).

How easy was it to give yourself an injection?

Not at all	A little	Moderately	Very	Extremely
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

How satisfied are you with **how often** you give yourself an injection?

Very dissatisfied	Dissatisfied	Neither dissatisfied nor satisfied	Satisfied	Very satisfied
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

How satisfied are you with the **time it takes to inject** the medication?

Very dissatisfied	Dissatisfied	Neither dissatisfied nor satisfied	Satisfied	Very satisfied
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Overall, how satisfied are you with your current way of taking your medication (self-injection)?

Very dissatisfied	Dissatisfied	Neither dissatisfied nor satisfied	Satisfied	Very satisfied
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Overall, how convenient is the self-injection device?

Very inconvenient	Inconvenient	Neither inconvenient nor convenient	Convenient	Very convenient
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

After this study, would you choose to continue self-injecting your medication?

Definitely not	Probably not	I don't know	Yes, probably	Yes, definitely
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

After this study, how confident would you be to give yourself injections at home?

Not at all	A little	Moderately	Very	Extremely
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Thank you for completing this questionnaire

ATTACHMENT 7: SELFDOSE SUBJECT QUESTIONNAIRE**SelfDose Subject Questionnaire**

The following questions ask about your feelings when using the SelfDose device in this study.

Please answer each question below by checking the box that best represents your opinion (Check only one box per question).

1. I liked being able to inject the medication at a speed that was comfortable for me.

Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly agree
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2. The design of the SelfDose handle made the device easy to use.

Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly agree
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3. I was able to easily tell when the SelfDose injection was finished.

Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly agree
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ATTACHMENT 8: ANTICIPATED EVENTS**Anticipated Event**

An anticipated event is an adverse event (AE; serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

For the purposes of this study the event of psoriasis will be considered an anticipated event.

Reporting of Anticipated Events

These events will be captured on the electronic case report form (eCRF) and in the database, and will be reported to the sponsor as described in Section 12.3.1, All Adverse Events. Any event that meets serious adverse event (SAE) criteria will be reported to the sponsor within the appropriate timeline as described in Section 12.3.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the sponsor will report these events in an expedited manner.

Anticipated Event Review Committee (ARC)

An Anticipated Event Review Committee (ARC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The ARC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The ARC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study drug.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan (ASMP).

INVESTIGATOR AGREEMENT

CNT0 1959 (guselkumab)

Clinical Protocol CNT01959PSO3006 Amendment 1

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

Signature: _____ Date: _____
(Day Month Year)**Principal (Site) Investigator:**

Name (typed or printed): _____

Institution and Address: _____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)**Sponsor's Responsible Medical Officer:**

Name (typed or printed): Philippe Szapary, MD, Vice President Immunology

Institution: Janssen Research & Development

Signature: _____ Date: 18-Nov-2016
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.